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VOLUME 29  
1934

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.





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## AVERTIN (TRIBROMETHANOL) ANESTHESIA IN NORMAL PERSONS

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Although the literature on avertin (tribromethanol) rectal anesthesia has become voluminous since the production of the chemical compound tribromethanol by Willstätter and Duisberg, in 1923, there are only a few investigations on the effects in normal persons of the drug administered alone, in the dosage used in basal anesthesia. Before we were willing to employ avertin anesthesia on a large scale in hospital practice, we deemed it advisable to investigate the effects of the drug in normal persons. The numerous reports recorded present either experiments on animals or observations on persons with such complicating factors as operation, auxiliary medication and supplementary anesthesia.

### METHOD

We studied avertin anesthesia in fifteen normal people with a view to obtaining information on the uncomplicated effects of the drug. We made observations on the following: age, sex, weight, dosage, constitution, pulse, temperature, respiratory rate and amplitude, condition of the reflexes, state of consciousness, presence of cyanosis and emesis, arterial and venous blood pressure, basal metabolism, complete blood chemistry, hematology and urinary findings. The observations were recorded: (1) in repose, immediately before the administration of the drug; (2) one hour after its introduction, when the anesthesia was at its height, and (3) four hours after its introduction, toward the end of the anesthesia. No auxiliary medication was given. In the studies avertin fluid was used, 1 cc. of fluid containing 1 Gm. of tribromethyl-alcohol and 0.5 Gm. of amylene hydrate. Solutions of avertin fluid were prepared according to the manufacturer's instructions in a 2.5 per cent solution in distilled water at a moderate temperature of from 95 to 104 F. (35 to 40 C.). The patients were healthy persons admitted to the surgical service for relatively minor operations—for the most part, inguinal hernioplasties. The operations were performed after the studies on avertin were completed. Little additional anesthesia was required for the operations, and there were no untoward effects.

### OBSERVATIONS

*Age, Sex, Dosage and Constitution.*—The first table gives the age, sex, weight and dosage of avertin and a few remarks on the complexion

From the surgical service of Dr. Harold Neuhoi and from the laboratories of the Mount Sinai Hospital.

and nervous make-up of the fifteen patients studied. There were ten men and five women. The youngest patient was 17 years of age, and the oldest 52. The weight varied between 105 and 160 pounds (48 and 73 Kg.). The average dosage of avertin fluid was 6.2 cc. One half of the patients were considered to be of a normal nervous make-up, one third excitable and the remainder phlegmatic.

*Pulse, Temperature, Respiration, Reflexes and Untoward Symptoms.*—Table 2 gives the pulse rate, temperature, respiratory rate and amplitude, condition of reflexes, state of consciousness and presence of untoward symptoms.

The average pulse rate before anesthesia was 73, the variations being between a low rate of 56 and a high rate of 96. After one hour of

TABLE 1.—*Age, Sex, Weight, Dosage and Constitution*

Case	Age	Sex	Weight, Pounds	Dosage, Amount Mg. per of Avertin Kg. Body Fluid, Weight Cc.		Com- plexion	Nervous Make-Up
1.....	52	M	148	100	6.8	Light	Phlegmatic
2.....	46	M	144	100	6.6	Light	Phlegmatic
3.....	43	M	160	100	7.3	Light	Excitable
4.....	39	M	105	100	4.8	Dark	Excitable
5.....	17	M	140	100	6.4	Dark	Normal
6.....	22	M	153	100	7.0	Dark	Normal
7.....	41	M	119	100	5.4	Dark	Excitable
8.....	26	M	129	100	5.8	Negro	Normal
9.....	48	M	159	100	7.2	Dark	Normal
10.....	17	M	120	100	5.4	Negro	Normal
11.....	46	F	160	100	7.0	Dark	Normal
12.....	37	F	130	100	5.8	Dark	Excitable
13.....	23	F	113	100	5.1	Light	Normal
14.....	48	F	133	100	6.0	Dark	Normal
15.....	30	F	140	100	6.3	Dark	Excitable

anesthesia the average pulse rate had risen to 89, with a low rate of 68 and a high rate of 110. In only two patients was there a fall in pulse rate at the end of one hour, and both of these were excitable people with pulse rates of 92 and 96 before anesthesia. At the end of four hours of anesthesia the average pulse rate was 83, an increase from the preliminary rate but a fall from the rate observed at the end of one hour.

The average rectal temperature before anesthesia was 99.1 F. At the end of one hour of anesthesia the temperature in every instance fell, the average temperature being 97.8 F. and the greatest fall 2 F. After four hours the temperatures in every case were still lower than the preliminary temperatures, but they tended to return to their original figures, the average temperature being 98 F.

The preliminary respiratory rate varied between 12 and 26, with an average of 16. After one hour of anesthesia the respiratory rate varied between 16 and 26, with an average of 22. There was a rise in respira-

tory rate in every case except one, in which instance the preliminary rate was 26, the highest recorded. At the end of four hours of anesthesia the average respiratory rate was 20.

TABLE 2.—*Pulse, Temperature, Respiration, Reflexes and Untoward Symptoms*

Case	Time	Pulse Rate	Temperature	Respiratory Rate	Respiratory Amplitude, Mm.	Condition of Reflexes, Corneal and Knee Jerk	State of Consciousness	Untoward Symptoms
1	Before anesthesia....	74	98.2	12	38	Present + +	Normal	
	1 hour of anesthesia.	110	98.3	16	Shallow	Absent 0	Absent	
	4 hours of anesthesia	72	97.0	17	31	Present +	Awake	Mucus
2	Before anesthesia....	69	98.0	13	35	Present +	Normal	
	1 hour of anesthesia.	95	97.2	19	25	Absent 0	Absent	Slight cyanosis
	4 hours of anesthesia	94	97.4	24	..	Present +	Asleep	Mucus Emesis
3	Before anesthesia....	64	99.0	17	27	Present + +	Normal	
	1 hour of anesthesia.	100	98.0	25	17	Absent 0	Absent	
	4 hours of anesthesia	80	97.8	22	..	Present + +	Awake	
4	Before anesthesia....	74	99.0	16	Deep	Present + +	Normal	
	1 hour of anesthesia.	102	97.8	24	Shallow	Absent 0	Awake	Slight cyanosis
							at end of 2 hours	Excitable and difficult to control at the end of 2 hours
5	Before anesthesia....	69	99.2	17	33	Present + +	Normal	
	1 hour of anesthesia.	83	97.2	22	18	Absent 0	Absent	
	4 hours of anesthesia	68	97.4	24	Shallow	Absent + +	Asleep	
6	Before anesthesia....	69	98.6	14	40	Present + +	Normal	
	1 hour of anesthesia.	90	97.2	20	29	Absent 0	Absent	Mucus
	4 hours of anesthesia	96	98.0	20	34	Present +	Awake	
7	Before anesthesia....	88	99.6	12	26	Present + +	Normal	
	1 hour of anesthesia.	96	97.8	16	22	Absent 0	Absent	
	4 hours of anesthesia	90	97.8	13	49	Present +	Awake	
8	Before anesthesia....	60	98.8	20	24	Present + +	Normal	
	1 hour of anesthesia.	63	97.2	20	26	Absent 0	Absent	
	4 hours of anesthesia	52	97.6	18	25	Present +	Asleep	
9	Before anesthesia....	68	98.6	15	42	Present +	Normal	
	1 hour of anesthesia.	74	98.0	24	29	Absent 0	Absent	
	4 hours of anesthesia	72	98.2	20	33	Present 0	Awake	
10	Before anesthesia....	56	99.2	20	38	Present +	Normal	
	1 hour of anesthesia.	78	97.2	20	27	Absent 0	Absent	
	4 hours of anesthesia	68	97.8	18	36	Present 0	Asleep	
11	Before anesthesia....	76	99.2	14	40	Present + +	Normal	
	1 hour of anesthesia.	84	98.2	24	24	Absent 0	Absent	
	4 hours of anesthesia	100	98.6	20	30	Present 0	Awake	Mucus Emesis
12	Before anesthesia....	92	99.8	26	25	Present +	Normal	
	1 hour of anesthesia.	76	98.4	22	27	Absent 0	Absent	Mucus
	4 hours of anesthesia	70	98.8	24	26	Present +	Awake	Emesis
13	Before anesthesia....	84	100.2	15	34	Present + +	Normal	
	1 hour of anesthesia.	84	99.0	26	23	Absent 0	Absent	
	4 hours of anesthesia	100	98.8	24	25	Present + +	Awake	
14	Before anesthesia....	86	99.0	17	32	Present + +	Normal	
	1 hour of anesthesia.	104	98.6	26	23	Absent 0	Absent	
	4 hours of anesthesia	122	98.8	18	..	Present + +	Asleep	
15	Before anesthesia....	96	99.8	17	34	Present + +	Normal	
	1 hour of anesthesia.	88	98.0	26	32	Absent 0	Absent	
	4 hours of anesthesia	82	98.0	24	..	Present + +	Asleep	
Averages								
	Before anesthesia....	73	99.1	16	35			
	1 hour of anesthesia.	89	97.8	22	25			
	4 hours of anesthesia	83	98.0	20	31			

The respiratory rate and amplitude were taken from the graphs of the basal metabolic readings. A typical graph is given. The figures for respiratory amplitude in table 2 are measurements in millimeters of the height of the respiratory curve in the basal metabolic graphs. In this way we were able to use exact measurements instead of such terms





Typical graph for the basal metabolic reading, showing respiratory rate and amplitude: Upper curve, before anesthesia; middle curve, after one hour of anesthesia, and lower curve, after four hours of anesthesia.

as deep and shallow. The average amplitude of respiration before anesthesia was 35 mm.; after one hour, 25 mm., and after four hours, 31 mm., representing a decrease at the end of one hour which was not quite made up at the end of four hours. Thus it can be seen that with an increase in the respiratory rate there is a decrease in the respiratory amplitude.

In these studies purely mechanical faults, such as a falling back of the tongue and jaw, were eliminated. Many of the reports in the literature of slow, shallow respirations were due to the unfavorable combination of avertin with the supporting narcotic.

In all of the cases corneal reflexes and knee jerks were absent at the end of one hour of anesthesia but in most of the cases had returned at the end of four hours. In studying the cases it was noted that the conjunctival and corneal reflexes disappeared first. Then a loss of muscular tension occurred and lastly a disappearance of tendon and skin reflexes. The pupils were at first narrow, and they dilated when struck by light. Then a state of contraction without reaction to light followed. The pupils next gradually dilated with a slow reaction to light, finally returning to their normal status. Pharyngeal and tracheal reflexes, as illustrated by inducing swallowing and cough, were preserved late.

At the end of four hours of anesthesia, nine patients were awake. The remaining patients, with the exception of one, had recovered from the primary anesthesia and appeared to be sleeping naturally. In one case the patient was excitable and difficult to control at the end of two hours.

Slight cyanosis was noted in two cases. In five cases there was an accumulation of a moderate amount of mucus in the pharynx. Vomiting in slight degree occurred in three cases. The uniform absence of sweating was of interest, in contrast to the usual profuse perspiration in inhalation and spinal anesthesia.

*Arterial and Venous Blood Pressure.*—Observations on the arterial and venous blood pressure are shown in table 3. In thirteen cases there was a drop in systolic blood pressure; in one case, a slight rise, and in one case, no change. The average systolic pressure before anesthesia was 113 mm. of mercury, with a high level of 140 and a low level of 96. At the end of one hour the average systolic pressure was 89 mm., with a high level of 108 and a low level of 68. At the end of four hours the average systolic pressure was 102 mm. with a high level of 118 and a low level of 70. The average fall in systolic pressure was 24 mm. for the determination at the end of one hour of anesthesia and 11 mm. for that at the end of four hours.

There were a drop in diastolic blood pressure in eleven cases, a rise in two cases and no change in two cases. The average diastolic pressure

before anesthesia was 71 mm. with a high level of 96 and a low level of 58. At the end of one hour the average diastolic pressure was 63 mm., with a high level of 90 and a low level of 54. At the end of four hours the average diastolic pressure was 66 mm., with a high level of 90 and

TABLE 3.—*Arterial and Venous Blood Pressure*

Case	Time	Systolic Pressure, Mm. Hg*	Diastolic Pressure, Mm. Hg*	Pulse Pressure, Mm. Hg*	Venous Pressure, Cm. H <sub>2</sub> O
1	Before anesthesia.....	108	78	30	6.5
	1 hour after anesthesia...	108	90	18	9.0
	4 hours after anesthesia..	108	80	28	9.0
2	Before anesthesia.....	102	76	26	5.0
	1 hour after anesthesia...	88	60	28	8.0
	4 hours after anesthesia..	80	50	30	5.0
3	Before anesthesia.....	122	80	42	5.5
	1 hour after anesthesia...	80	60	20	8.0
	4 hours after anesthesia..	110	68	42	3.0
4	Before anesthesia.....	106	60	46	8.5
	1 hour after anesthesia...	94	60	34	10.0 (strained)
	4 hours after anesthesia..	..	..	..	...
5	Before anesthesia.....	98	70	28	5.0
	1 hour after anesthesia...	100	70	30	10.0 (strained)
	4 hours after anesthesia..	104	70	34	...
6	Before anesthesia.....	98	60	38	9.0
	1 hour after anesthesia...	88	64	24	8.0
	4 hours after anesthesia..	110	76	34	8.0
7	Before anesthesia.....	120	60	60	3.0
	1 hour after anesthesia...	100	58	42	4.0
	4 hours after anesthesia..	110	60	50	...
8	Before anesthesia.....	110	70	40	8.0
	1 hour after anesthesia...	86	60	26	12.0 (strained)
	4 hours after anesthesia..	84	60	24	...
9	Before anesthesia.....	140	96	44	3.0
	1 hour after anesthesia...	68	54	14	4.0
	4 hours after anesthesia..	112	90	22	...
10	Before anesthesia.....	104	64	40	5.0
	1 hour after anesthesia...	84	58	26	8.0
	4 hours after anesthesia..	70	50	20	...
11	Before anesthesia.....	114	70	44	4.0
	1 hour after anesthesia...	88	54	34	4.0
	4 hours after anesthesia..	110	70	40	4.0
12	Before anesthesia.....	136	80	56	5.0
	1 hour after anesthesia...	100	70	30	3.5
	4 hours after anesthesia..	118	70	48	5.0
13	Before anesthesia.....	96	58	38	3.0
	1 hour after anesthesia...	80	58	22	4.5
	4 hours after anesthesia..	94	50	44	3.0
14	Before anesthesia.....	122	70	52	3.5
	1 hour after anesthesia...	100	60	40	3.5
	4 hours after anesthesia..	114	64	50	...
15	Before anesthesia.....	116	68	48	8.0
	1 hour after anesthesia...	78	64	14	7.0
	4 hours after anesthesia..	106	70	36	...
Averages	Before anesthesia.....	113	71	42	5.5
	1 hour after anesthesia...	89	63	26	6.9
	4 hours after anesthesia..	102	66	36	5.3

\* Mercury.

a low level of 50. The average fall in diastolic pressure was 8 mm. at the end of one hour and 5 mm. at the end of four hours.

It might be noted that the greatest drop in blood pressure (72 mm., systolic pressure; 42, diastolic pressure) was in case 9, which showed the highest blood pressure before operation.

The pulse pressure dropped in thirteen cases and rose in two. The average pulse pressure before anesthesia was 42 mm., with a high value of 60 and a low value of 26. At the end of one hour of anesthesia the average pulse pressure was 26, with a high value of 42 and a low value of 14. At the end of four hours the average pulse pressure was 36, with a high value of 50 and a low value of 20. The average fall in pulse pressure was 20 mm. in one hour and 6 mm. in four hours.

According to other observers (Anschütz, Specht and Tiemann,<sup>1</sup> Ransom<sup>2</sup> and Taylor and Lund<sup>3</sup>) the blood pressure almost uniformly drops, but the pulse pressure is changed only slightly. The fall in blood pressure is due to a paralysis of the vasomotor center. Our findings do not agree with those of Domrich,<sup>4</sup> who permitted experiments to be made on himself and who found that with avertin alone the blood pressure decreased only slightly.

The venous blood pressure rose slightly in ten cases, fell in three and remained unchanged in two. In three of the cases in which there was a rise there was straining when the needle was inserted into the vein. In eight cases determinations were not made after four hours of anesthesia. The average venous pressure before anesthesia was 5.5 cm. of water, with a high value of 9 and a low value of 3. At the end of one hour of anesthesia the average venous pressure was 6.9 cm., with a high value of 12 and a low value of 3.5. At the end of four hours the average venous pressure was 5.3 cm., with a high value of 9 and a low value of 3. There were an average rise of venous pressure of 1.4 cm. within one hour and an average fall of 0.2 within four hours. Venous pressures were determined by the direct method, the venous puncture being made in the median basilic vein of the left arm at a level with the heart.

According to Eyster,<sup>5</sup> the venous pressure under basal conditions in normal persons is usually from 4 to 6 cm. The upper limit of normal is 11 cm.

*Basal Metabolism.*—Studies of basal metabolism are shown in table 4. In six of the cases determinations were not made after four hours of anesthesia. In all of the cases the basal metabolism dropped.

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1. Anschütz, W.; Specht, K., and Tiemann, F.: Avertin Anesthesia in Surgery. *Ergebn. d. Chir. u. Orthop.* 23:406, 1930.

2. Ransom, H. K.: Avertin as an Anesthetic for General Surgery, *Arch. Surg.* 26:89 (Jan.) 1933.

3. Taylor, G. W., and Lund, C. C.: Blood Pressure Fall Occurring in Avertin Anesthesia. *New England J. Med.* 206:612, 1932.

4. Domrich: Action of Avertin on Circulation, *Zentralbl. f. Chir.* 55:2632, 1928.

5. Eyster, J. A. E.: Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929.

TABLE 4.—*Basal Metabolism*

Case	Before Anesthesia	1 Hour of Anesthesia	4 Hours of Anesthesia
1.....	— 5	—15	—11
2.....	—12	—28	....
3.....	+17	—19	....
4.....	0	— 8	....
5.....	+ 5	— 8	....
6.....	—10	—25	—13
7.....	+10	—23	0
8.....	+ 3	—24	—19
9.....	+ 2	—14	—12
10.....	— 7	—38	—16
11.....	+ 7	— 5	— 5
12.....	+33	— 7	—10
13.....	+12	—21	+ 2
14.....	— 6	—26	....
15.....	+16	— 3	....
Averages.....	+ 4	—18	— 9

TABLE 5.—*Blood Chemistry*

Case	Time	Urea, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Carbon Dioxide, per Cent of Volume	Choles- terol, Mg. per 100 Cc.	Choles- terol Ester, Mg. per 100 Cc.	Ester Con- tent, per Cent	Cal- cium, Mg. per 100 Cc.	Chlo- rides, Mg. per 100 Cc.
1	Before anesthesia.....	10	85	60.2	180	125	69	....	550
	1 hour of anesthesia.....	9	105	57.0	156	72	46	....	538
	4 hours of anesthesia....	10	70	55.0	144	50	34	....	561
2	Before anesthesia.....	16	100	57.5	310	200	65	13.6	526
	1 hour of anesthesia.....	13	100	52.5	350	225	64	12.6	535
	4 hours of anesthesia....	15	115	51.0	350	230	66	10.8	526
3	Before anesthesia.....	20	100	....	170	110	65	10.9	538
	1 hour of anesthesia.....	20	80	....	180	80	62	10.6	560
	4 hours of anesthesia....	19	78	....	130	70	54	....	515
4	Before anesthesia.....	11	75	56.5	120	75	63	10.4	492
	1 hour of anesthesia.....	13	75	51.5	125	70	56	10.0	468
5	Before anesthesia.....	24	75	52.5	290	145	50	10.5	550
	1 hour of anesthesia.....	24	95	54.0	285	150	53	10.6	560
	4 hours of anesthesia....	24	85	56.0	280	120	43	10.7	550
6	Before anesthesia.....	12	90	60.5	230	135	59	....	598
	1 hour of anesthesia.....	9	110	60.5	200	110	55	....	585
	4 hours of anesthesia....	10	90	58.5	200	115	57	....	585
7	Before anesthesia.....	12	120	58.0	220	105	47	10.4	527
	1 hour of anesthesia.....	13	130	57.0	190	105	55	10.4	504
	4 hours of anesthesia....	13	105	55.0	180	90	50	10.6	515
8	Before anesthesia.....	17	95	56.5	197	105	53	8.4	560
	1 hour of anesthesia.....	17	85	58.5	183	98	54	9.7	560
	4 hours of anesthesia....	15	80	56.5	160	100	63	10.6	560
9	Before anesthesia.....	14	90	61.0	260	106	41	9.5	525
	1 hour of anesthesia.....	20	95	60.0	268	164	61	9.8	540
	4 hours of anesthesia....	21	80	57.0	280	208	74	9.7	550
10	Before anesthesia.....	12	95	59.0	204	148	73	10.8	540
	1 hour of anesthesia.....	12	105	57.0	218	154	71	10.9	550
	4 hours of anesthesia....	13	80	59.0	200	143	72	10.9	535
11	Before anesthesia.....	9	105	57.5	210	156	74	7.5	575
	1 hour of anesthesia.....	9	115	55.5	200	148	74	10.5	565
	4 hours of anesthesia....	10	100	53.5	206	150	73	10.4	585
12	Before anesthesia.....	11	105	58.0	198	140	71	10.2	570
	1 hour of anesthesia.....	11	105	57.0	204	136	67	9.8	560
	4 hours or anesthesia....	12	120	55.5	190	136	72	9.9	550
13	Before anesthesia.....	13	95	50.0	145	104	72	9.7	585
	1 hour of anesthesia.....	13	95	47.5	136	89	65	9.7	555
	4 hours of anesthesia....	13	70	47.5	144	61	42	8.8	535
14	Before anesthesia.....	17	115	54.5	335	225	67	11.1	570
	1 hour of anesthesia.....	15	120	52.0	280	190	68	10.9	560
	4 hours of anesthesia....	10	110	55.0	310	200	65	10.3	525
15	Before anesthesia.....	18	95	52.0	210	160	76	10.4	550
	1 hour of anesthesia.....	16	100	50.0	210	145	69	10.4	570
	4 hours of anesthesia....	17	80	49.0	195	130	67	10.2	540
Averages									
	Before anesthesia.....	14	96	56.7	219	136	63	10.3	550
	1 hour of anesthesia.....	14	101	55.0	209	129	61	10.5	547
	4 hours of anesthesia....	14	90	54.5	212	129	59	10.3	545

The average basal metabolism before anesthesia was  $+4$  per cent, with a high value of  $+33$  and a low value of  $-12$ . At the end of one hour the average basal metabolism was  $-18$ , with a high value of  $-3$  and a low value of  $-38$ . At the end of four hours the average basal metabolism was  $-9$ , with a high value of  $+2$  and a low value of  $-19$ . The average fall in basal metabolism was 22 per cent in one hour and 13 per cent in four hours. The most marked fall in basal metabolism was in case 12, in which there was a fall of 40 per cent. The patient had a basal metabolism of  $+33$  before anesthesia.

The studies in basal metabolism were carried out with the Benedict-Roth apparatus. A characteristic basal metabolic graph is presented.

*Blood Chemistry.*—The blood chemistry is shown in table 5. The figures for urea were remarkably constant, there being no variations in the averages for the preliminary observation, nor for the observations made at the end of one and four hours. The individual variations were slight and were always within the margin of experimental error, and the resultant gives a flat figure of 14 mg. per hundred cubic centimeters of blood for all three periods.

Waters and Muehlberger<sup>6</sup> and Stander<sup>7</sup> found no significant changes in the figures for blood nitrogen, but the complicating factor of operation was present in Waters and Muehlberger's seven cases and that of supplementary narcotics in Stander's five cases.

The blood sugar showed a slight initial rise and a slight terminal fall, being 5 mm. per hundred cubic centimeters higher at the end of one hour than at the outset and 6 mm. lower at the end of four hours. The highest individual rise was 20 mm. after one hour of anesthesia, and the greatest fall, 25 mm. after four hours.

Under the conditions described in the papers of Waters and Muehlberger and Stander a rise in blood sugar was found. We can say that the rise in blood sugar is purely an effect of the avertin.

The carbon dioxide content of the blood showed a slight tendency to fall, the average figures being 56.7 volumes per cent at the preliminary determination, 55 volumes per cent after one hour of anesthesia and 54.5 volumes per cent after four hours. The total fall was 2.2 volumes per cent. This is a slight change. The greatest fall was 6.5 volumes per cent. In two cases the carbon dioxide content rose slightly. The lowest recorded figure is 47.5 volumes per cent.

According to Wymer and Fuss,<sup>8</sup> who studied four cases of avertin anesthesia, there were the following changes in the acid-base balance: The

6. Waters, R. M., and Muehlberger, C. W.: Tribromethanol Anesthesia, Arch. Surg. 21:887 (Dec.) 1930.

7. Stander, H. J.: Studies in Avertin. Am. J. Obst. & Gynec. 22:219, 1931.

8. Wymer, L. and Fuss, H.: Acid Base Balance and Pathologic Physiology in Avertin Narcoses, Deutsche Ztschr. f. Chir. 211:281, 1928.

alkali reserve (the carbon dioxide-combining power of the plasma) fell to below normal after the anesthesia; after varying periods of time it returned to, but did not exceed, the normal. There was never an increase of the alkali reserve above normal.

The reaction of the urine was shifted in the acid direction, the acidification lasting from twenty-four to forty-eight hours. The ammonia content of the urine was increased after the anesthesia; it fell, but did not reach normal within twenty-four hours. Wymer and Fuss concluded that the fall in alkali reserve with increased acidity of the urine and increased ammonia content was caused by true acidosis. Practically, the danger of acidosis is not great if the regulatory mechanism, particularly the kidneys and the respiratory center, are normal. In seven cases Achelis<sup>9</sup> found a lowering of the alkali reserve of from 2 to 6.6 volumes per cent.

The blood cholesterol averages were 219 mg. per hundred cubic centimeters for the preliminary reading, 209 mg. for the determination made after one hour, and 212 mg. for that made after four hours. The cholesterol esters were 136, 129 and 129 mg., respectively, for the same periods, representing an ester percentage of the total cholesterol of 63, 61 and 59 per cent, respectively. These figures were fairly constant.

We were particularly interested in these findings because of recent work showing the importance of the cholesterol and the cholesterol ester content of the blood plasma in determining hepatic damage (Thannhauser and Schaber<sup>10</sup> and Epstein<sup>11</sup>). The liver is the main excretory organ of cholesterol and regulates the relative content of cholesterol and cholesterol ester in the blood; 1 molecule of cholesterol is compounded with 1 molecule of fatty acid. In 100 cc. of normal human blood plasma there is from 150 to 200 mg. of total cholesterol, of which from 50 to 70 per cent is in the form of cholesterol ester. The aforementioned authors showed that in cases of hepatic damage the values for cholesterol ester were below those for free cholesterol, and that in the more severe cases the esters were much diminished or absent. The disappearance of the cholesterol ester occurs when the liver loses its ability to esterify the free cholesterol.

The figures for blood calcium showed little variation, the average figures being 10.3, 10.5 and 10.3 mg. per hundred cubic centimeters, respectively, for the preliminary determination and for the determinations made after one hour and after four hours.

9. Achelis: *Acid Base Relations and Operative Risk, Narkose u. Anaesth.* 11:541, 1928.

10. Thannhauser, S. J., and Schaber, H.: *Studies in Blood Cholesterol*, *Klin. Wchenschr.* 5:252, 1926.

11. Epstein, E. Z.: *Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases*, *Arch. Int. Med.* 50:203 (Aug.) 1932.

The chlorides in the blood were similarly constant, the average figures being 550, 547 and 548 mg. per hundred cubic centimeters, respectively, for the preliminary observation and for the determinations made after one hour and after four hours.

In summing up the changes in blood chemistry, we should say that the urea, cholesterol and cholesterol ester, calcium and chlorides did not change appreciably, and that a minimal early rise and subsequent fall in the sugar content and a slight fall in the carbon dioxide content took place.

*Plasma Volume.*—The plasma volume as determined by the hematocrit in twelve of fifteen instances showed a rise, which in the extreme instance reached 9 per cent (table 6). In only two instances was there a fall. The average rise from the preliminary determina-

TABLE 6.—Percentage of Plasma Volume

Case	Before Anesthesia	1 Hour of Anesthesia	4 Hours of Anesthesia
1.....	55	53	60
2.....	60	54	55
3.....	55	60	60
4.....	55	64	62
5.....	60	66	63
6.....	57	60	57
7.....	53	60	62
8.....	60	63	61
9.....	56	55	59
10.....	55	54	55
11.....	62	62	63
12.....	55	61	62
12.....	64	66	67
14.....	62	64	65
15.....	64	66	66
Averages.....	59	61	62

tion to that made after four hours was 3 per cent. In most instances the dilution was greater after four hours than after one hour, although this finding was not constant. The average figures are 59, 61 and 62 per cent, respectively, for the preliminary determination and for the determinations made after one hour and after four hours.

*Hematologic Studies* (table 7).—In this group five cases were studied. The determinations were made before anesthesia was given and again two hours after the administration of the avertin. There were no significant changes in the hemoglobin and in the number of red cells.

In three cases there was a rise in the platelet count, and in two a fall. The average platelet count was 266,000 before anesthesia, as compared with 287,000 after two hours of anesthesia. The difference is slight.

In one case there was leukocytosis, the white blood count rising from 8,000 to 14,200. In all other cases there were only minor changes.



TABLE 7.—Hematologic Studies

Case	Before Anesthesia	2 Hours of Anesthesia
7 Hemoglobin.....	102 per cent	104 per cent
Red blood cells.....	5,300,000	5,500,000
Platelets.....	310,000	260,000
White blood cells.....	8,800	14,200
Differential:		
Staff cells.....	5 per cent	5 per cent
Segmented cells.....	69 per cent	74 per cent
Eosinophils.....	0.5 per cent	1 per cent
Basophils.....	1 per cent	0 per cent
Lymphocytes.....	19.5 per cent	17 per cent
Mononuclears.....	5 per cent	3 per cent
Reticular cells.....	0.5 per cent	0.5 per cent
Coagulation time.....	10 minutes	4 minutes
9 Hemoglobin.....	92 per cent	93 per cent
Red blood cells.....	5,170,000	5,200,000
Platelets.....	220,000	245,000
White blood cells.....	8,200	6,350
Differential:		
Staff cells.....	11 per cent	4 per cent
Segmented cells.....	50 per cent	60 per cent
Eosinophils.....	5 per cent	8 per cent
Basophils.....	1 per cent	0 per cent
Lymphocytes.....	23 per cent	22 per cent
Mononuclears.....	10 per cent	6 per cent
Reticular cells.....	21 per cent	21 per cent
Coagulation time.....	7 minutes	5 minutes
10 Hemoglobin.....	89 per cent	87 per cent
Red blood cells.....	5,250,000	4,900,000
Platelets.....	250,000	250,000
White blood cells.....	6,400	4,600
Differential:		
Staff cells.....	2 per cent	2 per cent
Segmented cells.....	53 per cent	48 per cent
Eosinophils.....	..	6 per cent
Basophils.....	..	1 per cent
Lymphocytes.....	41 per cent	38 per cent
Mononuclears.....	4 per cent	5 per cent
Reticular cells.....	0.5 per cent	0.5 per cent
Coagulation time.....	7 minutes	4 minutes
11 Hemoglobin.....	85 per cent	84 per cent
Red blood cells.....	4,500,000	4,250,000
Platelets.....	200,000	290,000
White blood cells.....	7,800	8,000
Differential:		
Staff cells.....	4 per cent	8 per cent
Segmented cells.....	66 per cent	67 per cent
Eosinophils.....	..	1 per cent
Basophils.....	..	..
Lymphocytes.....	22 per cent	22 per cent
Mononuclears.....	8 per cent	2 per cent
Reticular cells.....	0.5 per cent	1 per cent
Coagulation time.....	4 minutes	4 minutes
13 Hemoglobin.....	83 per cent	85 per cent
Red blood cells.....	4,390,000	4,620,000
Platelets.....	350,000	420,000
White blood cells.....	7,600	7,200
Differential:		
Staff cells.....	..	4 per cent
Segmented cells.....	65 per cent	68 per cent
Eosinophils.....	3 per cent	1 per cent
Basophils.....	..	1 per cent
Lymphocytes.....	27 per cent	22 per cent
Mononuclears.....	5 per cent	4 per cent
Reticular cells.....	0.5 per cent	0.5 per cent
Coagulation time.....	4.5 minutes	1 minute

Finally<sup>12</sup> studied the white blood cells before and during avertin narcosis and found an increase in the total number of leukocytes. The average white cell count before the narcosis was 10,750, and during the narcosis, 16,600.

TABLE 8.—*Urinalysis*

Case	Time	Amount, Cc.	Specific Gravity	Reaction	Albumin	Sugar	Acetone	Diacetic Acid	Urobilin, Mg.	Microscopic
1	Before anesthesia....	150	1.014	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	200	1.010	Acid	0	0	0	0	0	Negative
2	Before anesthesia....	150	1.010	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	50	1.034	Acid	Trace	0	0	0	Faint trace	Few white blood cells
3	Before anesthesia....	75	1.032	Acid	Very faint trace	0	0	0	0	Negative
	4 hours of anesthesia	315	1.022	Neutral	Very faint trace	0	0	0	Faint trace	Negative
4	Before anesthesia....	175	1.020	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	75	1.044	Acid	0	0	0	0	0	Negative
5	Before anesthesia....	200	1.022	Alkaline	0	0	0	0	0	Negative
	4 hours of anesthesia	120	1.042	Acid	0	0	0	0	4.3	Moderate number of white blood cells
6	Before anesthesia....	110	1.020	Neutral	0	0	0	0	0	Negative
	4 hours of anesthesia	100	1.045	Neutral	0	0	0	0	Faint trace	Negative
7	Before anesthesia....	115	1.020	Acid	0	0	0	0	Faint trace	Negative
	4 hours of anesthesia	15	1.045	Acid	Faint trace	0	0	0	Faint trace	Few hyaline casts
8	Before anesthesia....	50	1.030	Acid	0	0	0	0	Faint trace	Negative
	4 hours of anesthesia	75	1.042	Acid	0	0	0	0	0	Negative
9	Before anesthesia....	100	1.022	Acid	0	0	0	0	Faint trace	Negative
	4 hours of anesthesia	75	1.040	Acid	0	0	0	0	Faint trace	Negative
10	Before anesthesia....	400	1.012	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	75	1.025	Acid	Very faint trace	0	0	0	0	Negative
11	Before anesthesia....	320	1.006	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	120	1.022	Acid	Very faint trace	0	0	0	0	Negative
12	Before anesthesia....	50	1.025	Acid	0	0	0	0	0	Negative
	4 hours of anesthesia	100	1.045	Acid	0	0	0	0	0	Negative
13	Before anesthesia....	300	1.006	Neutral	0	0	0	0	Trace	Negative
	4 hours of anesthesia	150	1.025	Acid	0	0	0	0	Trace	Negative
14	Before anesthesia....	120	1.015	Acid	Very faint trace	0	Trace	Very faint trace	Faint trace	Negative
	4 hours of anesthesia	120	1.015	Acid	Trace	0	Trace	Very faint trace	Faint trace	Negative
15	Before anesthesia....	150	1.020	Neutral	Very faint trace	0	0	0	0	Negative
	4 hours of anesthesia	50	1.022	Neutral	Very faint trace	0	0	0	0	Negative

The variations in the differential blood counts were neither constant nor marked. The tendency was toward a slight increase in the leukocytic elements and a slight decrease in the monocytic elements. In one

12. Finally, R.: Effect of Avertin on Liver Function, Beitr. z. klin. Chir. 149: 329, 1930.

case there was eosinophilia of 6 per cent in a patient who had had no eosinophilia before the anesthesia was given.

The reduction in the clotting time is of interest. This was a constant finding. The average clotting time before anesthesia was six and one-half minutes; two hours after anesthesia it was three and one-half minutes. We do not know the reason for this lowering of the clotting time. Changes in the platelet count or in the blood calcium content do not explain the finding in these cases.

Finally carried out studies of the coagulation time in thirty-eight cases. He found that it was decreased in twenty-seven cases, increased in five and unchanged in six. The average coagulation time before the narcosis was 10.2 minutes, and after the narcosis, 7.5 minutes. The decrease in the coagulation time was noted by another observer (La Cava<sup>13</sup>).

*Urine.*—The results of studies of the urine are shown in table 8. Examinations were made of specimens obtained before anesthesia and four hours after anesthesia. The average amount of urine secreted after four hours was 118 cc. The amount of urine before anesthesia, as given in table 8, was determined approximately four hours after the last voiding. There was an average decrease of about 50 cc. in the amount of urine after four hours of the avertin anesthesia.

Coincident with the relative oliguria, there was an increase in the specific gravity, the average before anesthesia being 1.018 and that four hours after anesthesia was started, 1.032. In four cases from a faint trace to a trace of albumin was found after four hours; this was not present before anesthesia. Sugar was absent in all of the cases. In one case acetone and diacetic acid were present, but they were present also before the anesthesia. In one case a few hyaline casts were found after four hours, and in two cases some white blood cells. In all of the cases the reaction of the urine after avertin was acid or neutral. In one case there was an appreciable amount of urobilin (4.3 mg.) in the urine after avertin anesthesia.

In his study of thirty-eight cases of avertin anesthesia, Finally found acetone and diacetic acid in three cases which did not show them before the anesthesia. In all of the cases the specific gravity of the urine was increased. Urobilinuria was occasionally observed.

#### SUMMARY

In this study of fifteen cases of avertin anesthesia in normal persons, uncomplicated by operation, auxiliary medication or supplementary anesthesia, the effects of avertin were:

1. An average increase in the pulse rate of 16 per minute and an average increase in the respiratory rate of 6 per minute.

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13. La Cava, G.: Clinico-Experimental Contribution to Basal Avertin Narcosis, *Policlinico (sez prat.)* 39:210 (Feb. 8) 1932.

2. A decrease in the amplitude of respiration.
  3. An average decrease of 1.3 F. in the rectal temperature.
  4. An average decrease in the systolic blood pressure of 24 mm.
  5. An average decrease in the basal metabolism of 22 per cent.
  6. An average decrease in the clotting time of three minutes.
  7. A slight early rise in the blood sugar, a slight fall in the carbon dioxide content of the blood and a slight rise in the plasma volume.
  8. A negligible change or no change in the venous pressure, blood cholesterol and cholesterol ester, blood calcium, blood chlorides and formed blood elements.
  9. Slight oliguria and an increase in the specific gravity of the urine.
  10. Loss of the conjunctival and tendon reflexes, with a late preservation of cutaneous and pharyngeal reflexes.
  11. Slight cyanosis in two instances, increase in the secretion of mucus in the pharynx in five instances and slight vomiting in three instances.
- No untoward effects followed the use of avertin in the dosage employed in basal anesthesia.

# GUNSHOT WOUNDS OF THE HEAD

AN ANALYSIS OF ONE HUNDRED AND FIVE CASES

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This series of 105 cases of gunshot wounds of the head was collected from the records of the Cincinnati General Hospital from 1922 to 1932. The total mortality rate (80.2 per cent) for 96 craniocerebral injuries of this series is considerably higher than that found for the same type of injury sustained during the World War. Cushing,<sup>1</sup> reporting a series of 219 cases in which operation was performed in a casualty clearing station, found a total mortality rate of 32.4 per cent, or, excluding 22 scalp wounds, 35.5 per cent for all craniocerebral injuries. Jefferson,<sup>2</sup> reporting from a base hospital, found no deaths in 91 cases of injury to the head without dural penetration and a mortality rate of only 37.6 per cent in 79 cases with dural penetration. Both considered only operative cases; however, every patient not moribund is said to have been subjected to operation. Horrax,<sup>3</sup> also reporting from a base hospital, operated on 93 of 132 patients with craniocerebral injuries, with a mortality rate of 37.6 per cent. He stated that 31 of the 132 injuries were cranial fractures without injury to the dura, which in part explains the low total mortality rate of 36.3 per cent for the entire series. This figure, 36.6 per cent, is comparable to the total mortality rate of 80.2 per cent for the 96 craniocerebral injuries reported in this paper. There is no such great difference in results, however, when the operative mortality rate for this series—45.1 per cent—is compared to the operative mortality rates mentioned earlier. As all patients reported in this series were alive on admission, and as every patient whose condition offered any possible chance of recovery was operated on, this series is comparable to that reported by Cushing. Since the operative mortality rate of all four series is essentially the same, the doubled total mortality rate of this series must be accounted for by the fact that the wounds were more severe or, more likely, that patients were seen earlier; many in this

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1. Cushing, Harvey: A Study of a Series of Wounds Involving the Brain and Its Enveloping Structures, *Brit. J. Surg.* 5:558 (April) 1918.

2. Jefferson: *Brit. J. Surg.* 7:262, 1919.

3. Horrax, G.: Observations on a Series of Gunshot Wounds of the Head, *Brit. J. Surg.* 7:10 (July) 1919.

series would never have lived to reach the casualty clearing stations of the war. Cushing stated that few were operated on within the first twelve hours after injury, and many after an interval of twenty-four hours. In this series there were only 8 admitted later than one hour after injury.

Many cases showed no improvement regardless of the supportive measures that were employed. Of the 77 patients who died, 42.8 per cent died within two hours of admission and 90.9 per cent within twenty-four hours. These two factors, the early admission and the early death of so many patients in this series, probably explain best the high total mortality rate.

#### MATERIAL

Every case of gunshot wound of the head brought to the receiving ward of the Cincinnati General Hospital is seen promptly by a member of the surgical house staff. If the patient is alive he is sent directly to the wards. Those who were dead on arrival or who died in the receiving ward are not reported in this series. All histories except 8 stated that the interval between injury and admission was one hour or less. An analysis of the material for this series is best made by consulting the following:

	Cases	Per Cent
Sex		
Male.....	94	89.5
Female.....	11	10.5
Race		
White.....	56	51.9
Colored.....	19	15.1
Cause of injury		
Suicide.....	55	53.2
Manslaughter.....	32	30.5
Accident.....	17	12.4
Details unknown.....	4	3.8

It is interesting to note that of the 56 persons who attempted suicide only two were female and none was colored. Often the type of firearm used is not mentioned, but by far the majority of the wounds were caused by pistol bullets fired at close range. In general, pistols of low caliber, such as .22 and .32, were used except when the police using the .38 caliber service pistol were involved.

#### ANALYSIS OF GROUPS

1. *Gunshot Wounds of the Head with the Dura Intact.*—There were 13 instances of this type of injury. Nine involved only the scalp or face and required only débridement of the wound with primary suture. There were no deaths from these superficial wounds. Four of the 13 showed a fracture of the skull. One of the 4 died on the second day from cardiac decompensation. This patient had attempted suicide because of heart failure. The bullet opened both frontal sinuses and

exposed the dura, but did not injure it. Under local anesthesia the edges of the skin and bone were excised, small folded rubber protective drains were placed in the frontal sinuses, and the skin was closed loosely with fine black silk sutures. The dura was not opened.

2. *Gunshot Wounds of the Head with Laceration of the Dura, But No Foreign Bodies in the Brain.*—There were 9 instances of this type of injury, with 8 operations and no deaths. The 1 patient not operated on was shot through the base of the nose, the bullet entering on the left side, crossing the right side of the face and ending just beneath the skin below and behind the right ear. At first no craniocerebral injury was suspected, but on the second day blood-tinged cerebrospinal fluid drained from the left nostril. The drainage of spinal fluid continued for three or four days and then stopped spontaneously. This case was complicated by the development of an arteriovenous aneurysm in the right side of the neck beneath the bullet. The bullet was removed, fortunately without opening the arteriovenous communication.

In every case prompt operation was performed, with thorough débridement of skin, bone and cortex and suture of the dura and skin without drainage. In 1 instance, the dural defect was so great that a piece of fascia lata was used to effect a closure.

3. *Gunshot Wounds of the Head with Subcortical Lodgment of Foreign Bodies.*—This is the largest group of the series. There were 49 cases with 42 deaths, a total mortality rate of 85.7 per cent. Only 15 of the 49 patients were operated on, with an operative mortality rate of 60 per cent. A study of the type of wounds in this group reveals several interesting facts. There were only 5 with tangential or gutter-like wounds, with detached fragments of bone driven into the brain. Of these 5, 4 recovered. The remaining 44 patients had a bullet or bullets retained within the skull. As might be expected from the few instances of the gutter type of wound and the high percentage of cases of suicide, most of the wounds were found in the temporal region at the level of the ear, usually just in front of it. Three patients recovered without removal of the penetrating bullet; 2 of these received débridement of the wound of entrance with no attempt to remove the bullet, and 1 received no operative treatment.

This group of cases, with a mortality rate of 85.7 per cent, offers a difficult problem. That many are hopeless from the start is shown by the fact that only about one third of the total number came to operation. Preoperative roentgenograms should be made in every case in order that the number and position of foreign bodies may be determined. It is well to have blood typing done for transfusion if possible. The operation itself consists of careful débridement of skin, muscle and bone. The removal of the whole fractured portion of the skull *en bloc* has

not been carried out in this series. It is not so important to excise the edges of the torn dura, although this tissue may have to be incised further to control bleeding from the cortex and to allow thorough exploration and cleansing of the track of the bullet in the cortex. The cortical wound is best handled by the technic described by Cushing.<sup>4</sup> A catheter attached to a sterile syringe is used alternately to irrigate and to suck the devitalized brain tissue from the track of the bullet.

Most surgeons explore the wound once with the gloved index finger to be sure that no foreign bodies have been overlooked. In this series, whenever the dura could not be closed with fine black silk, a strip was taken from the fascia lata and sutured to the edges of the dural defect. The wounds were closed without drainage in all the patients who recovered, closure consisting of interrupted sutures of medium black silk in the galea and interrupted sutures of fine black silk in the skin. A light cast for the head is helpful, because often the patient is restless and may derange the dressings or injure the unprotected brain.

4. *Through-and-Through Gunshot Wounds of the Head.*—There were 34 cases in this group with a mortality rate of 100 per cent. Only four were operated on, and these lived for an average of four hours after operation. Other reports on through-and-through wounds of the head give an average mortality rate of about 80 per cent, but this rate is based on only those cases in which the ventricles were not penetrated. Cushing found a 100 per cent mortality rate in cases showing penetration of one or both ventricles by fragments of bullets. In this series probably most through-and-through wounds were associated with the penetration of the ventricular system, because many of the patients attempted suicide and consequently were shot at close range through the midportion of the brain. Only 3 came to autopsy, but all of these showed perforation of one or both lateral ventricles.

*Immediate Complications.*—Infection is the most dreaded complication of gunshot wounds of the head. There were 3 patients with complicating infections in this series. They were not admitted for treatment immediately after sustaining the injury, 1 coming to the hospital four weeks after an incomplete débridement elsewhere, 1 coming for treatment thirty-six hours after injury and 1 being admitted sixteen hours after injury. There was no instance in the entire series of infection with *Clostridium Welchii*, although this complication was noted frequently in reports dealing with cranial injuries sustained during the World War. Meningitis developed in 2 patients.

4. Cushing, Harvey: Notes on Penetrating Wounds of the Brain, Brit. M. J. 1:221 (Feb. 23) 1918.



## REPORTS OF CASES

CASE 1.—J. S., a Negro, aged 25, was admitted to the Cincinnati General Hospital four weeks after having been shot by a .38 caliber pistol. The wound of entrance was in the right temporal region 2 inches (5 cm.) above the right ear; the wound of exit was 2 inches above the left eye. Superficial débridement with a suture of the skin was carried out in another hospital. The patient stated that he remained unconscious for four days and was discharged after two weeks. For the next two weeks he had a mild frontal headache. For ten days prior to admission, there had been a clear watery discharge from both nostrils.

On admission the patient was fully conscious, but somewhat confused. There were no visual disturbances and no weakness. The temperature was 99 F., and the pulse rate, 80. During his stay in the hospital only a slight amount of clear nasal discharge was noticed. Eight days before death, the patient became comatose and had a slight fever, but showed no localizing signs. Two days before death definite signs of meningitis developed; the spinal fluid showed gram-positive cocci and 2,000 polymorphonuclear leukocytes. A needle was inserted through one of the bullet wounds, but no abscess was located.

Autopsy revealed the right frontal sinus filled with pus communicating through several cracks with a large abscess in the right frontal lobe. There were also signs of early lobular pneumonia.

CASE 2.—L. E., a Negress, aged 13, was admitted to the Cincinnati General Hospital thirty-six hours after being shot with a .22 caliber pistol. The wound of entrance was just above and medial to the right eye. There was no wound of exit. The temperature was 100.2 F.; the pulse rate 128 and the respiratory rate, 22. The patient was comatose and showed unmistakable signs of meningitis. There was a continuous drainage of clear spinal fluid from the right nostril. Cisternal drainage was carried out, but the patient died the next day. Autopsy showed that the right cribriform plate had been perforated by the bullet, which was lodged in the brain just behind the optic chiasm. Early meningitis apparently took its origin from an abscess that surrounded the bullet.

CASE 3.—One patient who recovered was admitted to the hospital sixteen hours after receiving a gutter-like wound in the forehead. Débridement of the wound was performed under local anesthesia; the devitalized brain tissue was washed away, the bone fragments were removed, the dura was sutured as well as possible and the skin closed with fine black silk. An extradural infection developed which required treatment with surgical solution of chlorinated soda. The patient was discharged on the twenty-first day with a granulating wound of the forehead.

CASE 4.—One patient who had attempted suicide received a penetrating wound of the left side of the forehead. Thorough débridement, with removal of the fragments of bone and the devitalized brain tissue and transplantation of the fascia without drainage, was the surgical procedure. The bullet, shown by roentgenograms to be under the left temporal lobe, was not removed. On discharge five weeks after injury the patient showed no localizing signs, but there was definite mental instability. This mental instability has persisted for eleven years. It is not enough, however, to prevent the patient from doing housework. It manifests itself in crying spells, poor memory and a feeling that she is going to lose her mind. There is apparently no desire to repeat the attempt at suicide.

CASE 5.—In another case a fistula developed in the occipital region from which cerebrospinal fluid drained. The fistula developed eight days after operation and drained for two weeks without causing serious complications. The bullet was

flattened against the skull, the dura being punctured in one place by a sharply depressed fragment of bone. The puncture was closed with fine black silk sutures. There was no infection present at any time.

*Follow-Up Results.*—Because this series extends over eleven years and because many of the patients who survived were transients, the follow-up results are very disappointing. Only 4 patients could be found for reexamination. All 4 were classified in group 3, showing gunshot wounds of the head, with subcortical lodgment of foreign bodies. Two of the 4 still have bullets lodged in the brain (1 after ten years and 1 after eighteen months), but in neither of these are there any symptoms referable to the retained bullet. Two show hemiplegia, but this condition seems to be improving with exercise. There is no instance of headache, fainting or epileptic seizures. One patient who left the hospital with pronounced diplopia and sensory aphasia was completely relieved of symptoms in six months.

#### COMMENT

This study emphasizes the importance of considering the interval of time between injury and admission for treatment before drawing any comparisons as to total mortality rates in reports on gunshot wounds of the head. This is particularly true in comparing reports on injuries in the war, few of which were seen in the first twelve hours, with reports of gunshot injuries of the head encountered in civil life, of which the vast majority are seen in the hospitals within the first hour. The fact that of the 77 deaths reported here 90.9 per cent occurred in the first twenty-four hours shows how the amazing total mortality rate of 80.2 per cent can be found in a large municipal hospital, in which most injuries by gunshot are seen immediately after injury.

The high percentage of suicide, 53.3, is startling. If the figures are analyzed by years no marked increase is noted in the past four years. However, the largest number for any one year was found in 1932, in which there were 8 cases marked suicide, 4 marked accident and 2 marked manslaughter. It is likely that the high percentage of cases of suicide explains in part the relatively infrequent occurrence of the gutter type of gunshot wounds of the head (5) and also the high percentage of cases with retained bullets in the brain. Since the former is the most favorable and the latter the least favorable condition the total mortality rate of 85.7 per cent for gunshot wounds of the head with subcortical lodgment of foreign bodies is at least partially explained.

This study of cases reveals again the well known danger of infection in patients who are not operated on early. There was no instance of infection by *Cl. Welchii* probably because the operations were performed within the first few hours. There were 3 patients with cerebrospinal

rhinorrhea, 2 of whom died of meningitis; the other underwent no operation for the gunshot wound but recovered completely. In spite of the 1 recovery, cerebrospinal rhinorrhea should be considered as of grave prognostic significance.

Many authors believe that retained foreign bodies lead to traumatic epilepsy; some believe that foreign bodies should always be removed—if not at the primary operation, certainly at some later date. The follow-up data in this report are too meager to justify the expression of an opinion on this question, but 2 patients reporting for reexamination showed how difficult the decision of this question may be. One had had a bullet in the cranial cavity for over ten years, and the other for over one year, but neither showed any symptoms referable to the bullet. Both were told the first symptoms of intracranial pressure and were instructed to report to the hospital should any of the symptoms develop. Perhaps this is begging the question, but it is difficult to decide to perform a craniotomy to search for a bullet that is causing no demonstrable trouble.

#### SUMMARY

1. A study of 105 cases of gunshot wounds of the head is reported. Of these, there were 96 cases of craniocerebral injury.

2. The total mortality rate for the cases of craniocerebral injury was 80.2 per cent; for the 31 cases in which an operation was performed, it was 45.1 per cent.

3. All except 8 patients were admitted to the hospital within one hour after the injury. Of the 77 deaths, 42.8 per cent occurred within two hours and 90.9 per cent within twenty-four hours.

4. The high death rate in this series as compared with the statistics of the World War is undoubtedly due to the immediate hospitalization of all patients.

5. In this series of 105 cases, there were 56 attempts at suicide—53.3 per cent.

6. As recorded in all other studies, infection was the main cause of death among patients who did not die as a direct result of the injury.

# QUANTITATIVE STUDY OF THE RATE OF HEALING IN BONE

## I. DESCRIPTION OF METHOD

WILLIAM T. PEYTON, M.D.

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AND

CARL W. LAYMON, M.D.

MINNEAPOLIS

Some time ago (1929) it was decided to check the results of some experiments in which it had been reported that the rate of healing in bone could be influenced by certain variations in the experiment. Although careful studies have been carried out by different investigators to determine the influence of a certain substance or condition on the healing of bone, the conclusions drawn by these investigators are variable and in some instances in direct conflict. It appears probable that the cause of these conflicting results is due in large part, if not entirely, to the difficulty of estimating the amount of healing which has taken place at any given time after fracture has occurred or has been produced for experimental purposes. Clinically, it is impossible to be certain when a fracture is healed sufficiently to allow resumption of function. For this reason certain minimum limits of time have been set more or less arbitrarily for each type of fracture. These limits are based on the experience that angulation or displacement may occur if function is resumed earlier. The appearance of the repair as seen in roentgenograms is of value in observing the amount of repair and in estimating its strength, but since the method is based entirely on opinion, it is inaccurate. Several roentgenologists reading the same roentgenogram would give very different estimates of the strength of a given callus. Delayed union is also an unreliable measure of the healing of bone. There are various degrees of delayed union and a difference of opinion exists even as to when union is delayed. Nonunion is, of course, a definite entity when it does occur, but like delayed union it would serve only as a gross indicator when used to interpret experimental results.

In most experimental investigations the healing of bone has been based on the evidence of callus formation as seen in the roentgenogram. This gives no evidence of the early fibrous callus before calcium salts are deposited in it and an inaccurate estimate of the strength of the healing fracture later when calcium salts are being deposited.

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From the Department of Surgery, University of Minnesota.

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In most experimental investigations the healing of bone has been based on the evidence of callus formation as seen in the roentgenogram. This gives no evidence of the early fibrous callus before calcium salts are deposited in it and an inaccurate estimate of the strength of the healing fracture later when calcium salts are being deposited.

## METHOD

A method was therefore evolved to measure the strength of the callus throughout the healing process, as well as to determine when the healing process is complete. Since the first union is fibrous, it offers little or no resistance to a shearing force, but it does have tensile strength. Later, when calcium salts are laid down in the callus there is an appreciable resistance to shearing forces. The method evolved was therefore designed to measure tensile strength, resistance to bending and resistance to torsion.

To measure tensile strength it was necessary to devise a method of suspending the bone by one end and hanging weights on the other until the bone was broken. Resistance to bending and torsion in metal rods and beams is measured by the physicist and expressed as coefficients of bending and torsion. An attempt was made to determine the coefficients of bending and torsion for healing bone by the method and formula used for metal, but this was found impracticable because of the variable shapes of bones. It seemed that more reliable conclusions could be obtained by keeping the mechanical factors of the experiment as constant as possible and by treating the data obtained statistically. Certain modifications in the apparatus and method used by the physicist had to be worked out in order to adapt them to the process of measuring the ulna of the rabbit.

Since this study was begun quantitative studies concerning the resistance of healing bone to a shearing force have been reported by Lindsay and Howes<sup>1</sup> and by McKeown and others,<sup>2</sup> and a study of resistance to compression has been reported by Ross.<sup>3</sup>

*Material.*—Rabbits receiving the ordinary laboratory diet were used. No attempt was made to select animals of the same size, age, or weight. The ulna was used so that the radius would act as a natural splint, obviating the necessity of artificial splints for immobilization and permitting the animal to be about in normal fashion immediately after the bone was fractured.

1. Lindsay, M. K., and Howes, E. L.: *The Breaking Strength of Healing Fractures*, J. Bone & Joint Surg. **13**:491, 1931.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: *The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet*, Arch. Surg. **24**:458 (March) 1932. McKeown, R. M., Lindsay, M. K.; Harvey, S. C., and Lumsden, R. W.: *The Breaking Strength of Healing Fractured Fibulae of Rats: III. Observations on a High Fat Diet*, *ibid.* **25**:467 (Sept.) 1932; *The Breaking Strength of Healing Fractured Fibulae of Rats: IV. Observations on a High Carbohydrate Diet*, *ibid.* **25**:722 (Oct.) 1932; *The Breaking Strength of Healing Fractured Fibulae of Rats: V. Observations on a Low Calcium Diet*, *ibid.* **25**:1011 (Dec.) 1932.

3. Ross, Dudley: *A Method for the Production of Increased Compression Strength of Bones*, Brit. J. Surg. **22**:337, 1932.

*Technic.*—The technic of fracturing the bone was simple. The rabbits were anesthetized with ether, the hair was removed from one of the forelegs by means of barium sulphide, the skin prepared with iodine and alcohol, and the leg protected by a sterile drape. A longitudinal incision, about 3 or 4 cm. long, was made on the lateral aspect, the fascia was divided, and the muscles were retracted. The middle of the ulna was exposed and cut through by means of a sterile circular bone saw. As a rule no hemostasis was required, since there was little bleeding. The fascia and the skin were closed with interrupted linen sutures. The animals experienced little reaction from the procedure and behaved quite normally after one or two days. They were allowed to survive a varying number of days before they

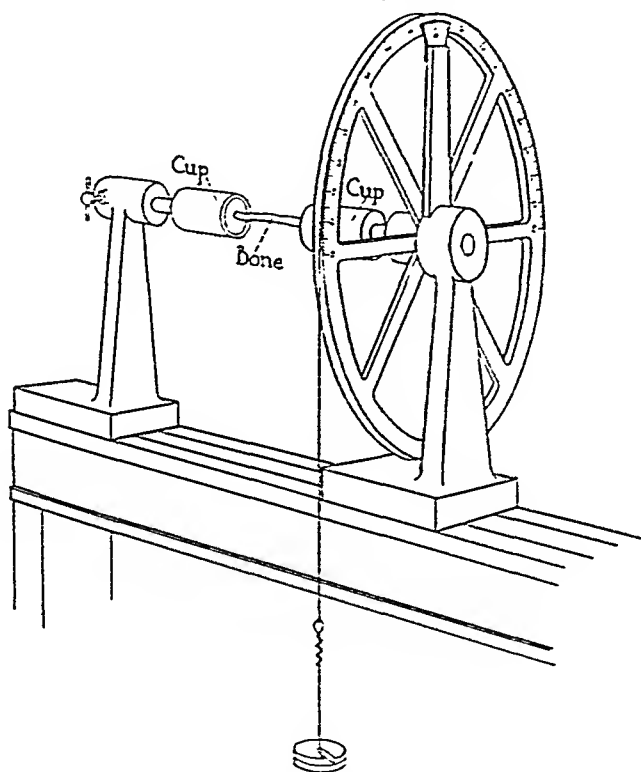


Fig. 1.—Method of measuring resistance to torsion.

were killed. Routine autopsy was not done, but rabbits in which evident intercurrent disease developed were discarded.

*Measurements.*—Both ulnas were removed, weighed and measured immediately after the animal was killed. As a rule the measurements were taken on the fractured and on the normal ulna of each rabbit. Occasionally, measurements could not be made on both ulnas for various reasons, such as an accident to one of the bones during the process of measuring, or infection of the fracture. The total length and the largest and smallest diameters at the middle of the bone were determined in centimeters by means of calipers. The average of the last two measurements was determined. A metal cup was then placed over each end of the bone and fixed firmly in place by means of plaster of paris. The cups were so constructed that they would fit in the apparatus for measuring torsion and could be



used in suspending the bone by one end and applying weight to the other in measuring breaking strength. After the bones had been placed in the cups, the length of the exposed bone, i. e., the distance between the inner edges of the cups, was measured. This distance was kept as constant as possible and, although recorded for most of the experiments, it was not utilized in the analysis of data.

*Torsion.*—In measuring torsion, the same apparatus as that used by the physicist to determine the coefficient of torsion in a metal rod was used (fig. 1). The cups were fitted into this apparatus while the plaster of paris was still soft, and they were left until it had set. Then weights were applied and readings were taken.

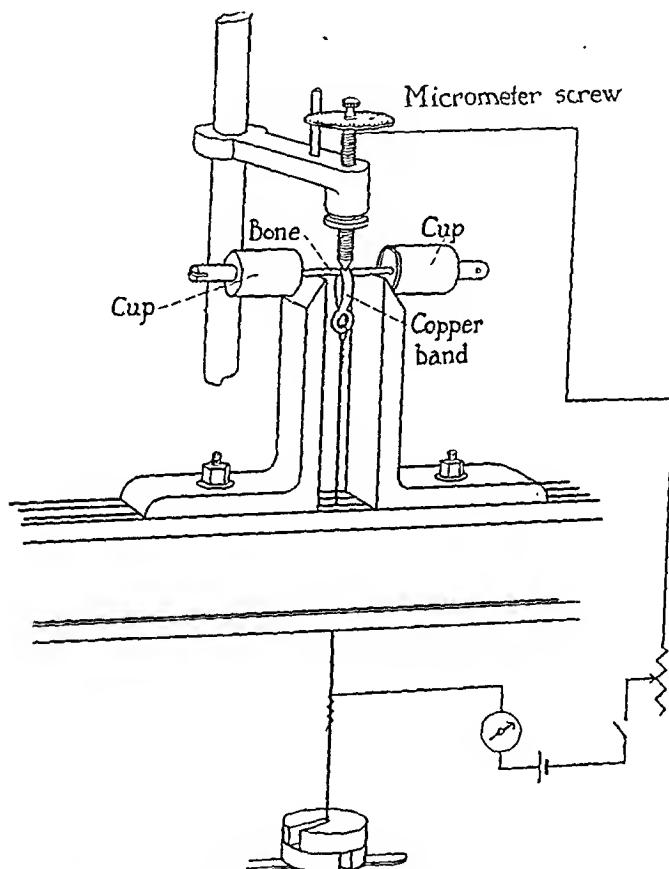


Fig. 2.—Method of measuring resistance to bending.

Readings were again taken as the weights were removed. For this part of the experiment it was important that the bones were firmly fixed in the cup, in order that no rotation could occur, and at the same time it was essential that the material used to fix the bone was removable. Plaster of paris seemed to fulfil these requirements better than any other material.

*Bending.*—The apparatus for measuring bending strength (fig. 2) consisted essentially of two parallel metal supports on which the bone rested and of a micrometer screw placed over the bone, which could be screwed down into contact with the bone, both before and after bending by the addition of a known weight. The weight was attached to a copper band hung over the bone at the midpoint between the rests. The number of revolutions or the part of a revolution of the

micrometer screw required to bring it against the bone determined the amount of bending. Turning the micrometer scale 1 degree moves its point approximately 0.005 mm. In order to be certain that the point of the micrometer screw was in contact with the bone the end-point was determined by establishing an electrical contact. This was accomplished by using electric current from a battery, one terminal of which was connected through a resistance to the micrometer screw and the other through a galvanometer to the copper band on which the weight was suspended. The supports were beveled so that the bone rested on very small

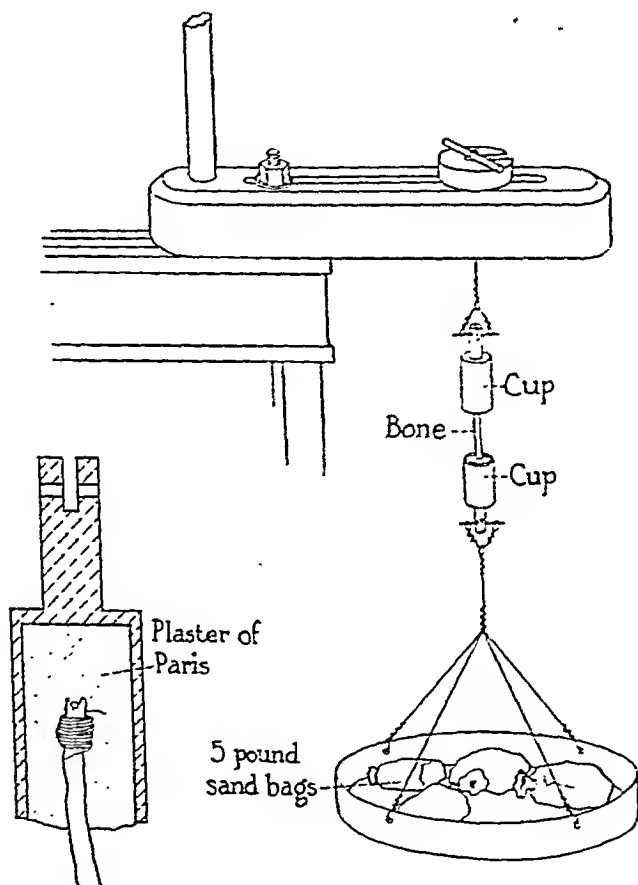


Fig. 3.—Method of determining tensile strength.

surfaces. The distance between these supports was kept constant. The bones were all placed in relatively the same position on the supports. The amount of bending was obtained both on adding and on removing weights.

*Tensile Strength.*—Tensile strength was ascertained in a rather simple manner (fig. 3). The metal cups were left in place and one of these was attached to a beam extending over the edge of the table, while a pan on which weights could be placed was attached to the other cup. Sacks of sand of 5 pounds (2.268 Kg.) each were added to the pan until the bone was broken. In some of the experiments the distal end of the ulna pulled out of the plaster, but it was found that this could be prevented by winding soft wire tightly around this end of the bone before it was embedded in the plaster of paris.

## RESULTS

Measurements were recorded on the right and left ulnas of thirteen rabbits taken without selection from the stock supply of animals. In this experiment only one reading each for bending and torsion was recorded. These readings were taken after adding 500 Gm. of weight. The results of the experiments are recorded in table 1.

TABLE 1.—Measurements on Right and Left Ulnas of Thirteen Rabbits

Right Ulna							Left Ulna						
Greatest Diameter	Least Diameter	Width of Cortex	Weight of Bone	Torsion	Bending	Breaking	Greatest Diameter	Least Diameter	Width of Cortex	Weight of Bone	Torsion	Bending	Breaking
0.55	0.22	0.05	2.032	0.4	0.50	62.0	0.56	0.22	0.04	2.020	0.4	0.30	89.00
0.49	0.23	0.01	1.167	0.5	1.50	79.5	0.50	0.23	0.06	1.210	0.5	2.0	89.75
0.48	0.20	....	1.666	1.0	3.75	59.5	0.50	0.21	0.07	1.556	1.4	3.75	69.50
0.45	0.22	0.03	1.124	0.6	6.00	34.0	0.46	0.21	0.06	1.092	1.2	2.0	39.00
0.52	0.28	....	1.282	0.6	2.00	30.0	0.49	0.20	....	1.220	0.7	5.0	35.00
0.54	0.25	0.01	1.637	0.6	0.50	55.0	0.56	0.27	0.06	1.707	0.6	1.5	24.00
0.54	0.28	0.04	1.517	0.6	4.50	59.5	0.55	0.27	0.04	1.545	0.5	2.5	64.50
0.50	0.24	0.09	1.462	0.5	2.00	97.5	0.49	0.26	0.08	1.532	0.4	2.5	97.50
0.48	0.26	0.06	1.425	0.4	1.25	69.0	0.40	0.28	0.08	1.422	0.3	1.5	97.50
0.47	0.23	0.05	1.110	0.9	3.50	48.0	0.48	0.24	0.07	1.286	0.9	7.5	94.00
0.50	0.26	0.06	1.691	0.7	4.50	54.0	0.50	0.27	0.05	.....	0.3	1.5	15.00
0.58	0.30	0.05	1.676	0.9	3.00	60.0	0.58	0.31	0.05	1.721	0.9	6.0	60.00
0.44	0.23	....	1.134	1.1	4.00	54.0	0.44	0.25	0.05	1.105	1.0	3.5	54.00

TABLE 2.—Statistical Constants for Right and Left Ulnas of Thirteen Rabbits\*

Dimension	Right Ulna Mean $\pm$ PE <sub>m</sub>	Left Ulna Mean $\pm$ PE <sub>m</sub>	Difference Mr - Ml	PE <sub>mr</sub> <sup>2</sup> + PE <sub>ml</sub> <sup>2</sup> (PE)	Difference PE	Right $\sigma$	Left $\sigma$
Greatest diameter	0.503 $\pm$ 0.0075	0.510 $\pm$ 0.0062	-0.007	0.0097	-0.721	0.0386	0.0322
Least diameter...	0.246 $\pm$ 0.0056	0.256 $\pm$ 0.0064	-0.010	0.0035	-1.176	0.0290	0.0326
Width of cortex...	0.056 $\pm$ 0.0039	0.063 $\pm$ 0.0026	-0.007	0.0047	-1.489	0.0171	0.0127
Weight of bone...	1.457 $\pm$ 0.0571	1.451 $\pm$ 0.0575	+0.006	0.0800	+0.075	0.2930	0.2826
Torsion.....	0.680 $\pm$ 0.0450	0.700 $\pm$ 0.0680	-0.020	0.0820	-0.244	0.2291	0.3488
Bending.....	2.850 $\pm$ 0.3280	3.040 $\pm$ 0.4000	-0.190	0.5170	-0.368	1.6825	2.0550
Breaking.....	60.920 $\pm$ 5.5350	64.520 $\pm$ 5.4320	-3.600	7.7550	-0.464	28.4281	27.9024

\* Mr represents the mean of measurements on the right leg; Ml, the mean of measurements on the left leg; PE<sub>mr</sub>, the probable error of the mean for measurements on the right leg; PE<sub>ml</sub>, the probable error of the mean for measurements on the left leg;  $\sigma$ , the standard deviation.

The statistical constants for these data (table 2) show that there is no significant difference between the right and the left ulna. This signifies that it is legitimate to use one leg as a control for experiments on the other.

Measurements have also been taken of a series of bones in which the right ulna was fractured and the left ulna used as a control. These results will be given in a later report.

# HEPATOLIENOGRAPHY

## EXPERIMENTAL STUDY OF THE ELIMINATION OF THE CONTRAST MEDIUM

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The development of an accurate, harmless method for the visualization of the liver and spleen has been for many years a challenge to the radiologist, internist and surgeon. Information about the size, shape, position, relation and structure of these organs would be of great value in the investigation and interpretation of almost all diseases of the abdominal viscera. If, in addition, it were possible to detect such pathologic conditions as neoplasms, abscesses, malformation, injuries and decreased, increased or abnormal function of these organs, many lives could be saved and much suffering alleviated by earlier and more exact treatment. It is, however, reasonable and necessary to insist that no matter how excellent the diagnostic method, it must not endanger the health or life of the patient.

Progress in the roentgen visualization of the liver and spleen has been made by the intravenous injection of iron preparations, the intravenous injection of dyes excreted by the liver and the intraperitoneal injection of air. Recently Oka<sup>1</sup> and Radt<sup>2</sup> described a new method of hepatolienography by the intravenous injection of a colloidal solution of thorium dioxide. Several hundred papers have appeared in the literature dealing with various phases of this method. A considerable difference of opinion exists as to the radioactivity, distribution and immediate and late toxic effects of this material. It seems to me that the most important point to consider in accepting or rejecting this method is to determine whether the thorium is eliminated, and, if eliminated, by what organs and at what rate. If the material is toxic, a reliable means must be devised for its rapid and complete elimination. The present work is based on a review of all the available literature on the use of thorium dioxide in hepatolienography and on a group of experiments by which it was believed possible to investigate the rate of elimination of thorium dioxide from the body.

1. Oka, M.: Eine neue Methode zur roentgenologischen Darstellung der Milz (Lienographie), Fortschr. a. d. Geb. d. Röntgenstrahlen 40:497, 1929.
2. Radt, Paul: Eine Methode zur roentgenologischen Kontrastdarstellung von Milz und Leber, Klin. Wchnschr. 8:2128, 1929.

## REVIEW OF THE LITERATURE

While it has repeatedly been considered that thorium is eliminated by the lungs through cells contained in the bronchial mucus, by the liver through the bile, by the intestines through the feces and by the kidneys through the urine, nevertheless no definite proof or quantitative studies have been reported of actual adequate elimination by any organ. Oka,<sup>1</sup> in his original study of hepatolienography, by means of colloidal thorium dioxide noted severe hemoglobinuria in rabbits. The urine from these animals contained small amounts of thorium. It is possible that the thorium in the urine was derived directly from the blood plasma. In a later article, Oka<sup>3</sup> does not suggest the presence of any method of elimination of thorium either in animals or in man. Radt,<sup>2</sup> in his first descriptions of hepatolienography by the use of thorium, did not consider the problem of elimination. In a late contribution he<sup>4</sup> summarized his experiences of three and a half years of experimental hepatolienography with thorium dioxide in animals and two years of clinical work with seventy patients. No definite diminution in the intensity of the roentgen shadow of the liver and spleen could be detected in experimental animals eighteen months after the injection of the thorium. Patients observed over a long period showed no decrease in the density of the roentgen shadow of the liver or spleen. He concluded that both roentgen examination and histologic studies indicate a slow process of elimination by an unknown method. Dickson<sup>5</sup> believed that in rabbits the shadow of the liver is reduced 50 per cent in intensity during the first three months after the injection. He suggested that cells containing the granules of thorium are eliminated by passing into the lungs, after which they are carried to the exterior in the bronchial mucus. The same method has also been considered by Radt<sup>6</sup> and Kadrnka.<sup>7</sup> No diminution in the quantity of thorium stored in the spleen, bone marrow, lymph nodes and ovaries occurred in three months.

3. Oka, M.: *Klinische Anwendung der "Lienographie," einer neuen Methode zur roentgenologischen Darstellung von Milz und Leber*, Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:892, 1930.

4. Radt, Paul: *Zur Kontrastdarstellung von Leber und Milz (Hepato-Lienographie)*, Therap. d. Gegenw. **75**:348, 1932.

5. Dickson, W. H.: *Thorotrast: A New Medium for Radiologic Diagnosis*, Canad. M. A. J. **27**:125, 1932.

6. Radt, Paul: *Ueber die körnige Ablagerung kolloider Farbstoffe in den Leberparenchymzellen von Kaninchen nach intravitaler Injektion (nach Versuchen mit Tusche und Eisen)*, Ztschr. f. d. ges. exper. Med. **69**:721, 1930.

7. Kadrnka, Silvijs: *Hepatosplenographie: méthode radiologique d'exploration du parenchyme hépatique et splénique par introduction intraveineuse de "Thorotrast," substance colloïdale à base de dioxyde de thorium*, Schweiz. med. Wchnschr. **61**:425, 1931.

Bungeler<sup>8</sup> observed definite roentgen shadows of the liver and spleen in animals twenty-one months after the injection of thorium. He did not recommend the use of thorium in hepatolienography so long as no information is available as to how long the thorium is retained. Kadrnka<sup>9</sup> considered the elimination of thorium from both experimental animals and man as very slow. The roentgen shadows produced by the thorium persisted for many months. The lungs were considered a possible means of elimination, but the rôle of the liver and kidneys could not be determined. Stewart<sup>10</sup> did not observe any evidence of a decrease in the intensity of the roentgen shadow of the liver and spleen in a patient observed for eight months. Naegeli<sup>11</sup> made microscopic examinations of the liver and spleen eighteen months after the injection of thorium into experimental animals. No decrease in the quantity of thorium granules was observed. Popper<sup>12</sup> injected thorium intravenously into twelve patients, four of whom were examined at necropsy. In one patient who died two months after the injection, a chemical analysis showed 97 per cent of the thorium present in the liver and spleen, while 3 per cent was recovered from the bone marrow. Examination of patients who had received injections of thorium four months previously and of animals which had received injections seven months previously showed no diminution in the roentgen shadow of the liver or spleen. Leipert<sup>13</sup> made a chemical analysis of the thorium contents of various organs of experimental animals and of man. He found that patients who received injections two, four and sixty days previous to necropsy showed 64.3, 56.9 and 97 per cent of thorium in the spleen, liver and bile. Rabbits receiving injections twenty-eight, sixty-seven and ninety-eight days previous to examination showed 48.5, 98.9 and 70.8 per cent of thorium in the liver, spleen and lungs. He concluded that detached reticulo-endothelial cells containing thorium are eventually lodged and retained in the spleen. The possibility of elimination through the liver by means of the bile

8. Bungeler, W., and Krautwig, J.: Ist die Hepato-Lienographie mit Thorotrast eine unschädliche diagnostische Methode? *Klin. Wchnschr.* **11**:142, 1932.

9. Kadrnka, Silvijs: Hepatosplenography, Roentgenologic Demonstration of the Parenchyma of the Spleen and Liver by Means of a New Intravenous Contrast Medium (Thorotrast), *Radiology* **18**:371, 1932.

10. Stewart, W. H.; Einhorn, Max, and Illick, H. E.: Hepatography and Lienography Following the Injection of Thorium Dioxide Sol (Thorotrast), *Am. J. Roentgenol.* **27**:53, 1932.

11. Naegeli, Lauche: Ueber experimentelle und pathologisch-anatomische Untersuchungen bei Kontrastdarstellung der Milz und Leber, *Med. Klin.* **28**:1878, 1931.

12. Popper, H. L., and Klein, Erwin: Ueber Hepato-Lienographie, München, *med. Wchnschr.* **78**:1829, 1931.

13. Leipert, Theodor: Ueber die Verteilung des Thorium im Organismus nach Injektion von Thorotrast, *Wien. klin. Wchnschr.* **44**:1135, 1931.

was considered greater than through the kidneys. Einhorn<sup>14</sup> injected thorium dioxide into seven patients. No definite evidence of elimination could be detected by roentgen studies of the liver and spleen. Whitaker<sup>15</sup> observed no diminution in the shadow of the liver in a patient six months after the injection of thorium dioxide. It appears from the literature that roentgen studies, microscopic observations and chemical examinations of organs, bile, sputum, feces and urine furnish no evidence of a physiologic mechanism for the adequate elimination of thorium dioxide from the body.

#### METHOD AND RESULTS OF EXPERIMENT

Twenty rabbits were used in this investigation. The animals varied from 1,625 to 3,200 Gm. in weight. In each animal 2.5 cc. of colloidal thorium dioxide per kilogram of body weight was injected intravenously. All the injections were made with aseptic technic in the veins of the ear, but in some animals it became necessary to use the veins in the extremities. Roentgen examinations were made of the living animals at irregular intervals, and of the organs at necropsy. All the roentgenograms were made by a standard technic. The animals were kept on the usual diet.

*Roentgen Observations.*—Group I: Preliminary studies were made on ten rabbits. Roentgenograms were made on the first, seventh, fifteenth, thirtieth, and forty-fifth days after the last intravenous injection of the thorium dioxide. All roentgenograms taken twenty-four hours after the last intravenous injection of 2.5 cc. of colloidal thorium dioxide per kilogram of body weight showed the liver and spleen as smooth, clearcut shadows of homogeneous density. The position, size, shape and margins of the organs were accurately outlined. In some animals the spleen showed small punctate areas of increased density, especially near the periphery. In the roentgen shadows of the liver it was possible, in a few animals, to see a fan-shaped area which apparently represented the course of the larger vessels. Roentgenograms taken fifteen, thirty and forty-five days after the injection showed no evidence of definite diminution in the density of the hepatic and splenic shadow. In the small animals it was also possible to observe definite shadows produced by the kidneys, suprarenal glands and marrow of the larger bones. When more than 10 cc. of colloidal thorium dioxide per kilogram of body weight was injected distinct roentgen shadows were produced by the lungs, suprarenal glands, kidneys and marrow of the larger bones.

Group II: In rabbits 7 (male, weighing 1,800 Gm.) and 2 (male, weighing 1,860 Gm.) roentgenograms of the liver and spleen were made twenty-four hours after the intravenous injection of thorium dioxide. One daily intravenous injection of 100 cc. of 0.9 per cent saline solution was given for fourteen consecutive days. Roentgen examinations were then made on the following day, and fifteen and

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14. Einhorn, Max; Stewart, W. H., and Illiek, H. E.: Experiences with Uroselectan Sodium, Skiodan and Thorotrast, M. J. & Rec. **134**:56, 1931.

15. Whitaker, P. H.; Davis, T. B., and Murgatroyd, F.: Hepato-Lienography by the Aid of Thorotrast; Its Uses and Dangers, Quart. J. Med. **5**:34, 1933.

thirty days later. The roentgenograms taken on the first, fifteenth and thirtieth days after the injection of 100 cc. of 0.9 per cent saline solution showed no evidence of any diminution in the size, shape and density of the shadow obtained twenty-four hours after the injection of thorium dioxide.

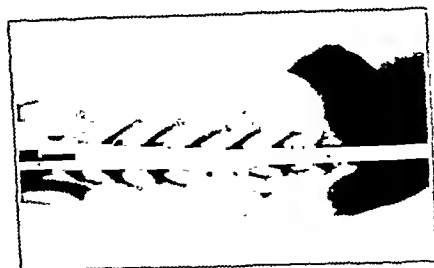


Fig. 1 (rabbit 36).—Hepatolienography forty-five days after a total intravenous injection of 10 cc. of a colloidal solution of thorium dioxide per kilogram of body weight.



Fig. 2 (rabbit 36).—Roentgenogram of the liver, spleen, lungs, kidneys, suprarenal glands and right posterior extremity forty-five days after the injection of thorium dioxide.



Fig. 3 (rabbit 31).—Hepatolienography forty-five days after the intravenous injection of 2.5 cc. of thorium dioxide per kilogram of body weight.

Group III: In rabbits 9 (female, weighing 2,025 Gm.) and 13 (female, weighing 2,250 Gm.) roentgen examination of the liver and spleen was made twenty-four hours after the injection of thorium dioxide. The animals were given one daily intravenous injection of 100 cc. of 10 per cent solution of dextrose for fourteen consecutive days. Roentgen examinations were then made on the first, fifteenth and thirtieth days. The roentgenograms taken after the injection



of 100 cc. of 10 per cent solution of dextrose for fourteen consecutive days showed no apparent diminution in the density of the shadow produced by the liver and spleen twenty-four hours after the injection of thorium dioxide.

Group IV: In rabbits 1 (male, weighing 2,540 Gm.) and 12 (female, weighing 2,530 Gm.) roentgenograms of the liver and spleen were made twenty-four hours after the intravenous injection of thorium dioxide. One daily intravenous injection of 100 cc. of a 5 per cent solution of calcium chloride in 0.9 per cent saline solution was given for fourteen consecutive days. Roentgen examination was made on the following day and fifteen and thirty days later. There was no evidence of any diminution in the intensity of the roentgen shadow of the liver and spleen following the intravenous injection of solution of calcium chloride for fourteen consecutive days.



Fig. 4. (rabbit 7).—Hepatolienography forty-five days after the intravenous injection of 2.5 cc. of thorium dioxide per kilogram of body weight and fourteen daily intravenous injections of 0.9 per cent saline solution.



Fig. 5 (rabbit 7).—Roentgenogram of the organs removed at necropsy, forty-five days after the intravenous injection of thorium dioxide and thirty days after the intravenous injection of saline solution.

Group V: In rabbits 14 (male, weighing 2,700 Gm.) and 3 (female, weighing 2,740 Gm.) roentgenograms of the liver and spleen were made on the day following the intravenous injection of thorium dioxide. One daily subcutaneous injection of 0.2 cc. of combined typhoid vaccine was given for fourteen consecutive days. Roentgen examination was made on the following day and fifteen and thirty days later. Following the subcutaneous injection of 0.2 cc. of typhoid vaccine for fourteen consecutive days roentgen examination of the liver and spleen showed no evidence of any diminution in the size, shape and density of the shadow obtained twenty-four hours after the intravenous injection of thorium dioxide.

Group VI: In rabbits 16 (female, weighing 2,540 Gm.) and 17 (female, weighing 2,250 Gm.) roentgenograms of the liver and spleen were made twenty-four

hours after the injection of thorium dioxide. The animals received one daily subcutaneous injection of 0.25 cc. of epinephrine for fourteen consecutive days. Roentgen examination was made on the following day and fifteen and thirty days later. There was no definite evidence of any diminution in the roentgen shadow of the liver and spleen following the subcutaneous injection of 0.25 cc. of epinephrine as compared with the density of the shadow obtained twenty-four hours after the injection of thorium dioxide.

*Microscopic Study.*—Sections of the liver, spleen, suprarenal glands and kidneys were made from the animals in group I, one, fifteen, thirty and forty-five days after the injection of thorium dioxide. All the sections were stained with hematoxylin and eosin. The granules of thorium were observed in the reticulo-endo-



Fig. 6 (rabbit 12).—Hepatolienography forty-five days after the intravenous injection of 2.5 cc. of thorium dioxide per kilogram of body weight and thirty days after fourteen daily intravenous injections of a 5 per cent solution of calcium chloride in 0.9 per cent saline solution.

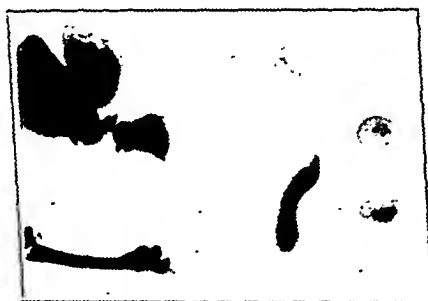


Fig. 7 (rabbit 12).—Roentgenogram of the liver, spleen, lungs, kidneys, suprarenal glands and right tibia forty-five days after the intravenous injection of a solution of calcium chloride.

thelial cells of the spleen, liver, suprarenal glands and lungs, while in the kidneys the granules of thorium were located in the cells of the glomerular tuft. The thorium was not stained and appeared as highly refractive small granules. There was no evidence of any diminution in the quantity of the granules of thorium in the phagocytic cells of the liver, spleen, suprarenal glands or kidneys forty-five days after the intravenous injection. Microscopic examination of the liver, spleen, suprarenal glands, lungs and kidneys from the animals in groups II, III, IV, V and VI forty-five days after the intravenous injection of the thorium dioxide showed no distinct evidence of any diminution in the amount of granules of thorium in the liver, spleen, lungs, suprarenal glands or kidneys as compared with the amount of granules of thorium found in the same organs of the animals in group I.

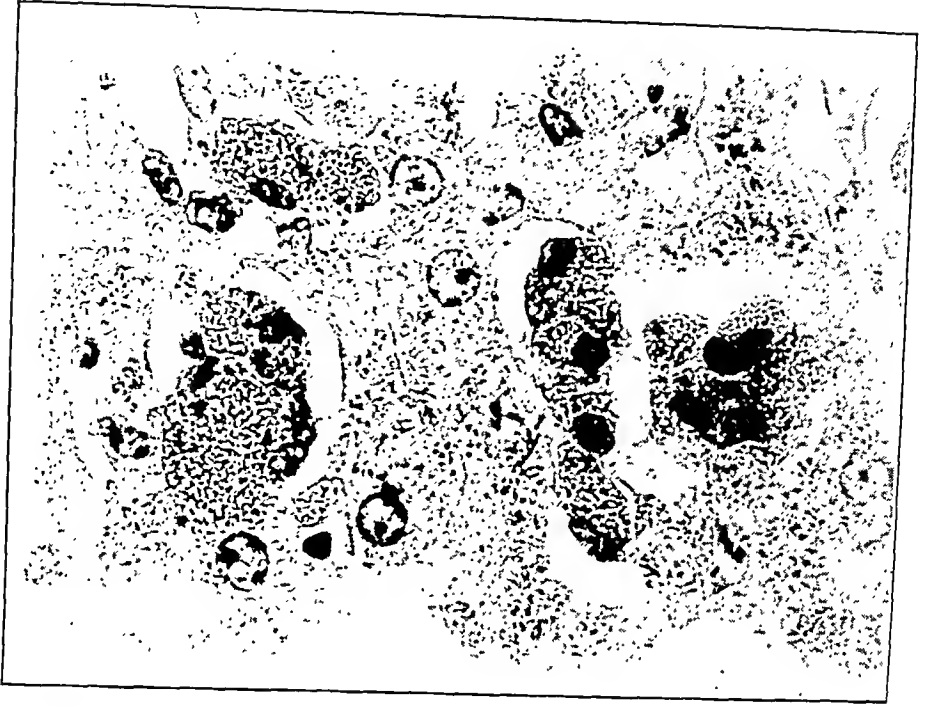


Fig. 8.—Granules of thorium in the Kupffer and hepatic cells;  $\times 800$ .

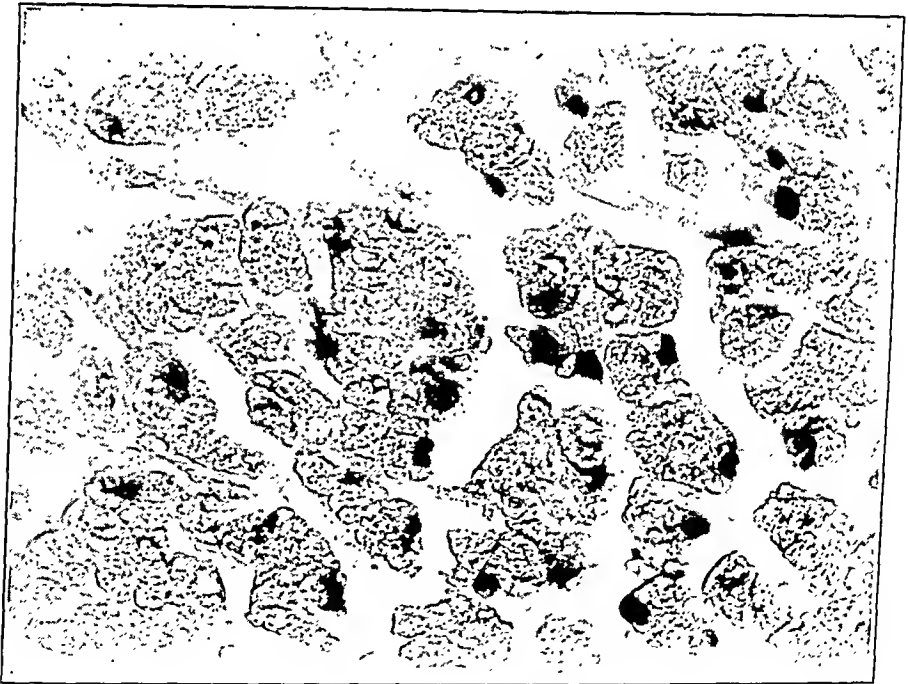


Fig. 9.—Granules of thorium in the reticulo-endothelial cells of the spleen;  $\times 800$ .

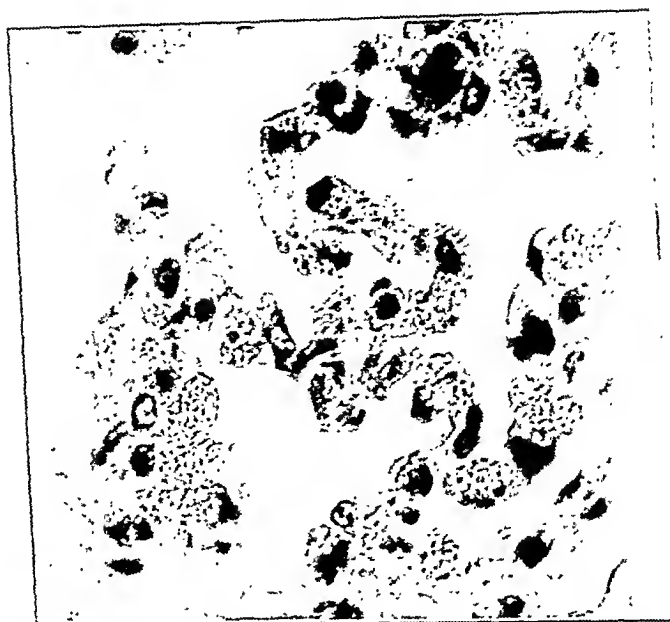


Fig. 10.—Granules of thorium in the phagocytic cells of the lungs:  $\times 800$ .

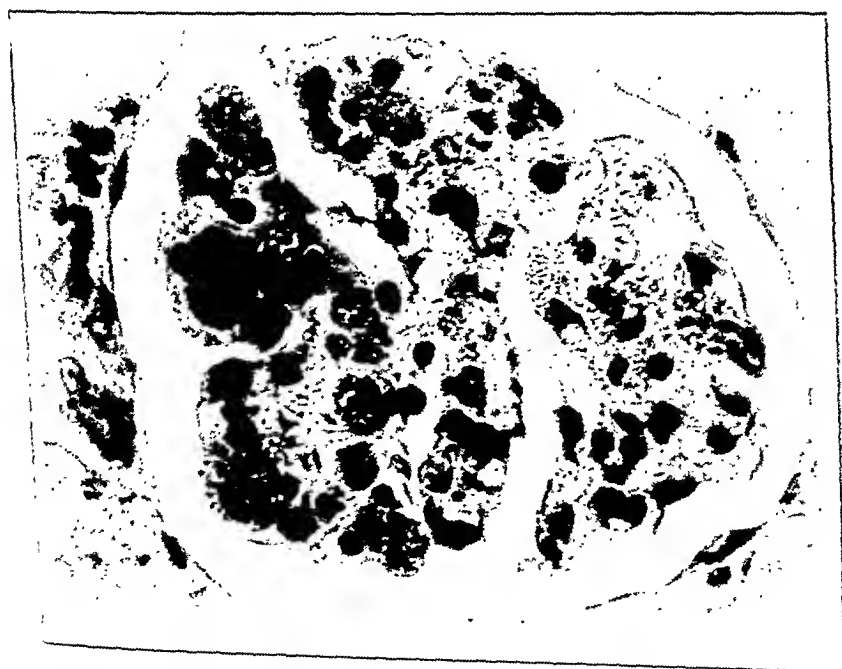


Fig. 11.—Granules of thorium in the phagocytic cells of the glomerular tuft;  $\times 800$ .

## COMMENT

The thorium preparation used in this work consisted of a stabilized solution of thorium dioxide which contained 25 per cent of thorium dioxide by volume and about 20 per cent of thorium by weight. The material mixed well with the blood and was injected in divided doses without any difficulty or immediate reaction. The animals appeared normal during the entire period of observation.

Following an intravenous injection granules of thorium are rapidly removed from circulation. No granules of thorium could be detected in the plasma five minutes after the first intravenous injection of 2.5 cc. of colloidal thorium dioxide per kilogram of body weight. The thorium is removed from the circulation by the anchored phagocytic cells of the reticulo-endothelial system. The importance of this efficient mechanism for removing particulate material from the circulating blood has been investigated by numerous workers. Goldman<sup>16</sup> was apparently the first to emphasize the importance of, and call attention to the widespread distribution of, a system of cells in various organs of the body which have essentially the same function. It remained, however, for Aschoff<sup>17</sup> to present the collected evidence that there exists in the body an anatomically extensive and functionally important group of highly differentiated cells which manifest such striking similarities in their reactions to vital stain and granular material as to warrant their consideration as a unit. An unusual peculiarity of the constituent cells of this system is their distribution in a number of organs such as the spleen, liver, bone marrow, medulla of the suprarenal gland and lungs instead of localization in a definite fixed circumscribed area. According to Aschoff the basis for the inclusion of a cell or cell group as a portion of the reticulo-endothelial system is the marked ability to phagocytose rapidly and to retain granular material. Aschoff used the term "reticulo-endothelial system" in a limited and in a broad sense. In the limited sense it is composed of two groups of cells: (1) the reticulum cells of the splenic pulp, the cortical nodules and pulp cords of the lymph nodes and the lymphoid apparatus; (2) the reticulo-endothelial cells of the sinuses of the capillaries of the bone marrow, the suprarenal cortex and the hypophysis. In a broad sense the constituent cells of the reticulo-endothelial system include the reticulum cells, the reticulo-endothelial cells, the tissue histiocytes and the phagocytic monocytes of the circulating blood.

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16. Goldman, E.: Die äussere und innere Secretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," *Beitr. z. klin. Chir.* **64**:1, 1909.

17. Aschoff, Ludwig: Ueber die Lipoidinfiltration in den Kupfferschen Sternzellen und in den Retikulumzellen der Milz, und Beziehungen zu den Xanthelasmaen, *Ber. d. Naturw. gesellsch. z. Freiburg* **20**:66, 1913.

While the physiology of the reticulo-endothelial system is not well understood, Aschoff,<sup>18</sup> Maximow,<sup>19</sup> Schittenhelm<sup>20</sup> and Jaffe evaluate the function of the reticulo-endothelial system as the most important factor in all general defensive reactions. It is the only mechanism by which particulate material such as bacteria, pigment and dead cells can be removed from the circulation. The phagocytic reticulo-endothelial cells located in the liver, spleen, bone marrow and lungs remove the greater portion of thorium from the blood stream. Smaller quantities are phagocytosed by the reticulo-endothelial cells of the suprarenal glands, ovaries and kidneys. The dispersion and deposition of the particles of thorium cannot be controlled after they reach the circulating blood. The location of the thorium depends on its direct contact with and phagocytosis by the reticulo-endothelial cells of the various organs. The liver, spleen and bone marrow possess the largest divisions of the reticulo-endothelial system and will, under normal conditions, phagocytose the largest number of particles of thorium. The density of the roentgen shadow is in direct proportion to the quantity of thorium in the cytoplasm of the reticulo-endothelial cells of the organ. The liver, spleen and bone marrow present, therefore, a denser shadow than the lungs, suprarenal glands, kidneys or ovaries. The roentgenograms of the liver, spleen, bone marrow, kidneys and suprarenal glands made forty-five days after the intravenous injection of thorium showed no difference in the density of the shadows when compared with similar films taken twenty-four hours, fifteen and thirty days after the injection of thorium dioxide. The microscopic examination of the liver, spleen, lungs, suprarenal glands and kidneys fifteen, thirty and forty-five days after the injection of thorium dioxide showed no evidence of a decrease in the quantity or redistribution of the thorium as compared with similar examinations twenty-four hours after the injection. It was believed possible by intravenous or subcutaneous injection of various substances to stimulate any existing process of elimination and to observe any redistribution of the particles of thorium present in the reticulo-endothelial cells of the various organs. However, even after the daily intravenous injection of 100 cc. of a 0.9 per cent saline solution for fourteen days it was not possible to detect any immediate or late roentgen evidence of any diminution in the quantity of thorium in the liver, spleen or other organs. The density of the roentgenograms made forty-five days after the

18. Aschoff, Ludwig: Das reticulo-endotheliale System, *Ergebn. d. inn. Med. u. Kinderh.* 24:1. 1924.

19. Maximow, Alexander: *Macrophages or Histiocytes: Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, p. 426.

20. Schittenhelm, A.: Normale und pathologische Physiologie des reticulo-endothelialen Systems, in *Handbuch der Krankheiten des Blutes und der Blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 2, p. 492.

injection of thorium was identical with that of films made twenty-four hours after the injection. Similar observations were made after the use of a 10 per cent solution of dextrose, a 5 per cent solution of calcium chloride, typhoid vaccine or epinephrine. Not only the roentgenograms of the liver and spleen of the live animals, but those of the organs removed at necropsy produced shadows of identical density, regardless of the time which had elapsed. The microscopic studies showed an approximately similar quantity and location of the granules of thorium in the cytoplasm of the reticulo-endothelial cells of the various organs when compared with the observations in the control group (I). Since the intensity of the shadow of the liver and spleen produced by the thorium depends on the presence of the granules of thorium in the reticulo-endothelial cells of those organs, it is evident that if the reticulo-endothelial cells are not actively phagocytic or injured, the smaller amount of material would be phagocytosed and the roentgen shadow would be less intense. It appears from this investigation that the particles of thorium are permanent inclusions.

While the reticulo-endothelial system has important functions, the effects of the thorium have to be considered not only as the direct effect on the reticulo-endothelial cells, but also as possible indirect functional effects on the cells of the organs of which the reticulo-endothelial cells are only a part. Thus the effect of the thorium on the liver cannot be considered as limited to the Kupffer cells, since possible effects on the hepatic cells and their function must be weighed. This consideration becomes especially important when one observes the presence of particles of thorium in such important and sensitive structures as the suprarenal glands and ovaries. While thorium has not been considered radioactive by some investigators, doubt entertained in this regard by competent workers makes it necessary to realize fully that once thorium is phagocytosed by the reticulo-endothelial cells, it is apparently permanently fixed in the body. The thorium cannot be eliminated or redistributed by the means used in this experiment. The realization that the thorium remains fixed in the reticulo-endothelial cells should emphasize the careful selection of cases for the use of this material. The intravenous injection of large doses for diagnostic purposes ought to be limited to patients in whom, after every other diagnostic method has been exhausted, the additional information proves the necessity for immediate surgical treatment.

#### CONCLUSION

Marble-like roentgen shadows of the liver and spleen of rabbits can be obtained by the intravenous injection of 2.5 cc. of colloidal thorium dioxide per kilogram of body weight. The thorium is removed from the circulation by the phagocytic reticulo-endothelial cells located prin-

cipally in the liver, spleen and bone marrow. Some thorium is deposited in the lungs, suprarenal glands, kidneys and ovaries. Roentgen and histologic examination showed no evidence of elimination or redistribution of thorium in ten rabbits forty-five days after the injection. Fourteen daily injections of 100 cc. of a 0.9 per cent saline solution, a 10 per cent solution of dextrose, a 5 per cent solution of calcium chloride, 0.2 cc. of combined typhoid vaccine or 0.25 cc. of epinephrine did not eliminate or redistribute the thorium dioxide. Since the health and life of the patient may be jeopardized by the prolonged presence of particles of thorium in the vital organs, the intravenous injection of thorium dioxide for diagnostic purposes should be restricted until some positive method of rapid elimination has been discovered.



# ACCESSORY ARTICULAR PROCESSES OF THE LUMBAR VERTEBRAE

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WHEELING, W. VA.

In these days of traumatic injuries and subsequent legal entanglements it is of considerable importance for the surgeon and roentgenologist to know about possible anomalies of the skeletal system and to be able to distinguish them from supposed fractures. Improved roentgenographic technic allows one to visualize a given bone with much more detail than was possible in the not too distant past. Hence it is a natural tendency to diagnose a demonstrated separation of continuity in a bone as a fracture if the history of an accident makes such a diagnosis plausible. This applies especially to alleged fractures of processes of the vertebrae. For technical and anatomic reasons the articular processes of the vertebrae are difficult to demonstrate. It is here that misinterpretation may not infrequently be met with and discussions arise as to whether an abnormal condition is present and, if so, whether the abnormality represents a traumatic or a congenital lesion.

In 1933, Rendich and Westing<sup>1</sup> (to the best of our knowledge, for the first time in the American literature) called attention to an abnormality of the articular processes of the lumbar vertebrae, which they described as a "separate ossicle occurring at the lower end of the inferior articular processes of the second and third lumbar vertebra"; they added five cases of their own to the two cases previously reported in the German literature. Undoubtedly findings of this sort have been encountered in every roentgen laboratory, but they were probably always diagnosed as fractures, if circumstances warranted it.

It may be well to review the known facts concerning the diagnosis of accessory articular processes of the lumbar vertebrae. In 1931, at the twenty-second congress of the German Roentgen Society, Reisner,<sup>2</sup> presented a paper entitled "How to Distinguish Normal, Inflammatory

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From the Wheeling Clinic.

1. Rendich, R. A., and Westing, S. W.: Accessory Articular Process of the Lumbar Vertebrae and Its Differentiation from Fracture, *Am. J. Roentgenol.* **29**:156, 1933.

2. Reisner, A.: Unterscheidungsmerkmale normaler, entzündlicher und post-traumatischer Zustände an der Wirbelsäule, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **44**:726 (Dec.) 1931.

and Post-Traumatic Conditions of the Spine." In the paper he mentioned a case in which a gap across the right lower articular process of the second lumbar vertebra was accidentally found. There was no history of trauma, and the patient did not complain of pain in the back. Because of the perfectly smooth outline of the edges of the bone and the absence of displacement of the distal fragment, and of atrophy. Reisner considered the case one of an accessory articular process. In his discussion of the case. Grashey stated that he had seen the same abnormality several times, and that he differentiated it emphatically from a fracture.

In the same journal appeared a paper by Müller,<sup>3</sup> describing a case of formation of a gap through the left lower articular processes of the second lumbar vertebra. Four weeks previous to the examination, the patient had fallen down a flight of stairs; the examination was undertaken to find a possible cause of the indefinite pains in the back. In this first publication Müller considered the finding to be an *Umbauzone*, the result of an injury with attempted repair through formation of connective tissue in the bone. One year later, in a second publication—after hearing Reisner's paper and Grashey's discussion, we venture to say—Müller<sup>4</sup> reconsidered the diagnosis and felt inclined to look at the case as an anomaly—an accessory articular process. In February, 1933, Rendich and Westing published the reports of five cases of formation of a gap through the lower articular processes of the lumbar vertebrae; they expressed the opinion that they were dealing with congenital lesions rather than fractures. In two of their cases no history of trauma was obtainable. Two patients received a possible injury to the back on the day of the examination, and another patient had received one four days before. All of the patients, however, complained of vague pains in the back with various localizations, and all had various degrees of limitation of motion. The roentgenograms of the spines of all of the five patients showed gaps through one or two articular processes, with well defined, smooth, regular edges of cortical density. Although an old ununited fracture may give a similar picture, three of Rendich and Westing's patients had sustained injuries only a few hours or days previous to the examination, and it seems impossible that such changes, if due to a fracture, could have taken place within such a short interval. Therefore the diagnosis of fracture as a cause for the gaps seems unreasonable. Since there is no recognized separate epiphysis for the development of the tip of the articular process,

3. Müller, Walther: Spaltbildungen an Gelenk- und Dornfortsätzen der Wirbelsäule auf der Basis von Umbauzonen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 44:644, 1931.

4. Müller, Walther: Ueber eine bemerkenswerte Form von Wirbelsäulenmissbildung, *München. med. Wchnschr.* 79:356 (Feb. 26) 1932.

Rendich and Westing could classify their findings only as accessory ossicles at the articular processes.

The aforementioned publication brought to mind a case we saw in October, 1932.

CASE 1.—A man, aged 49, a railroad employee, who, in October, 1931, was hit in the back by a slowly moving car, was referred to us for roentgenograms of the lumbar vertebrae and pelvis. He did not tumble over and, except for a short passing pain at the site of the impact, had no unusual sensations. He paid no attention to the accident and went on working without further complaint. After three months he began to notice vague pains in the back, which continued. He sought medical advice, but the pain did not yield to various methods of treatment.

The roentgenologic findings on Oct. 10, 1932, were as follows: The right and left lower articular processes of the third lumbar vertebra showed a distinct gap about 1 mm. wide and slightly curved, which was seen more clearly on the right than on the left, where the spinous process was somewhat overlapping. The smaller lower fragments were about 8 mm. in length. The bony edges of the larger and smaller fragments at the gap were perfectly smooth and showed cortical density. The smaller fragments did not present atrophy of the bone, displacement or evidence of formation of callus or of a spur of bone. The axis of the spine was straight. The only other pathologic finding in the spine was that the first sacral vertebra showed nonunion of the posterior arch.

With the history of the previous accident, the diagnosis was ununited fractures of the lower articular processes of the third lumbar vertebra and spina bifida occulta.

On reading Rendich and Westing's paper, we were struck with the similarity in roentgenologic appearance between their cases and the one reported here; the fact that our patient mentioned that he had no immediate pains in the back and had worked for three months after the accident without complaints increased our doubts as to whether we had diagnosed the condition correctly. In summary, the following facts presented themselves: The patient had received an injury to the back. The spine was not immobilized after the injury. After one year a roentgenogram showed complete separation of continuity in the bone substance of two articular processes of the third lumbar vertebra. There was no indication of callus formation, nor was there formation of a bony spur. Because the spine was not immobilized and because the patient was working, it might be assumed that union of the fractures did not occur, and that we had to deal with a case of pseudo-arthritis. The smoothed edges of the fragments suited this diagnosis. From these data alone it was therefore possible to assume that during the accident the patient had received fractures of the lower articular processes of the third lumbar vertebra. In 1923, Koch<sup>5</sup> published the report of a case with the same end-results, except that a diagnosis of

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5. Koch, Konrad: Die isolierten Gelenkfortsatzbrüche der Lendenwirbelsäule, Deutsche Ztschr. f. Chir. 180:339, 1923.

fracture was made immediately after the accident and there was a slight displacement of the fragment. The fracture did not heal, but the edges of the fragments of bone became smoothed out. The patient

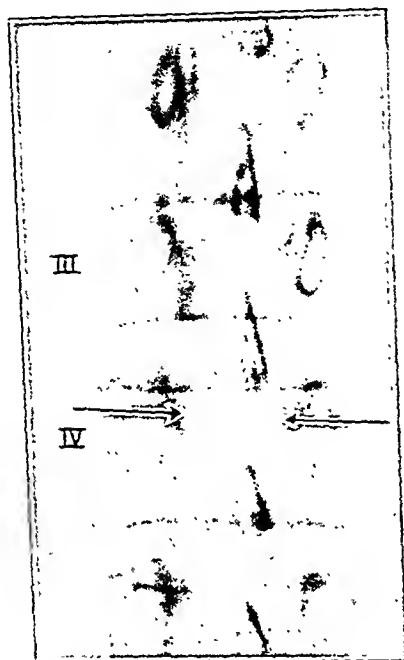


Fig. 1.—Formation of gap through the lower articular processes of the third lumbar vertebra.

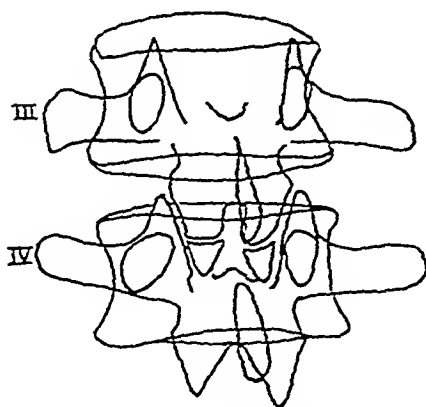


Fig. 2.—Diagram of the roentgenographic findings in case 1.

refused to be operated on and continued to complain of an indefinite "pain in the back."

On the other hand, there were features in our case which cast doubt on the diagnosis of fracture and made us lean toward the diagnosis of congenital malformation. It is reasonable to assume that an injury

severe enough to fracture two articular processes would give rise to immediate and pronounced symptoms, but they were absent and the man continued at his work. Koch reported that his patient was in a state of severe shock after the injury. One would also expect to find at least an irregularity, if not a displacement, of the small separated tips of the

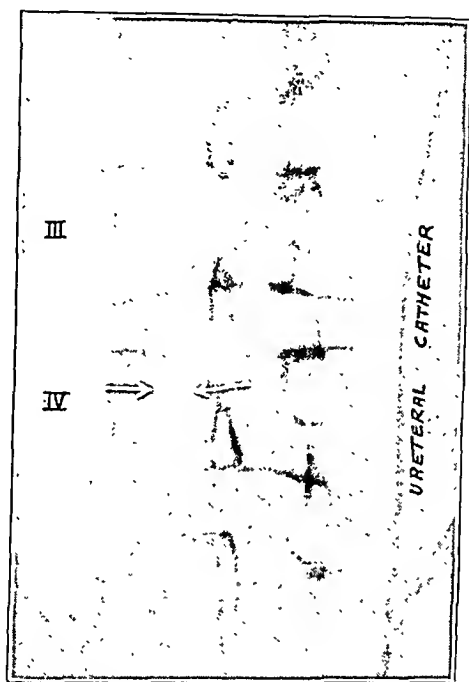


Fig. 3 (case 2).—Formation of a gap through the right lower articular process of the third lumbar vertebra.

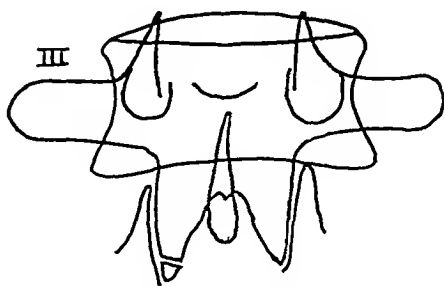


Fig. 4.—Diagram of the roentgenographic findings in case 2.

articular processes. Instead, their position was normal. Furthermore, the small, broken-off fragments might have shown atrophy after one year, but they were just as dense as the rest of the articular processes. In addition, the spine, as seen in both views, was straight. The finding of a spina bifida occulta in roentgenograms might give a hint as to the possibility of further developmental defects.

After a review of all of these facts and the arguments pro and con, it seemed that it might be impossible to convince the patient that he had only a congenital lesion of the third lumbar vertebra. In a legal case it might be just as impossible to demonstrate to a jury that there

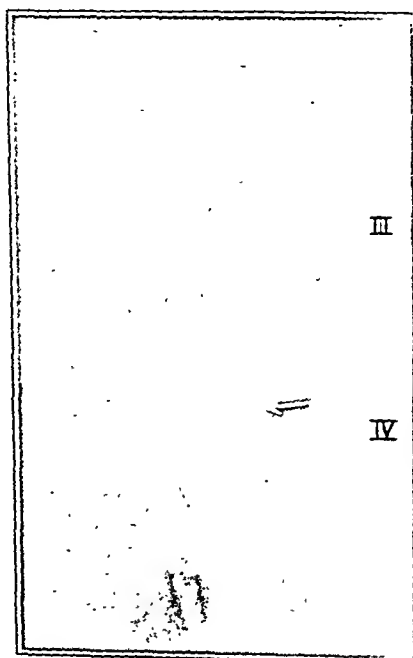


Fig. 5 (case 2).—Oblique view, with the patient rotated 45 degrees on the right side.

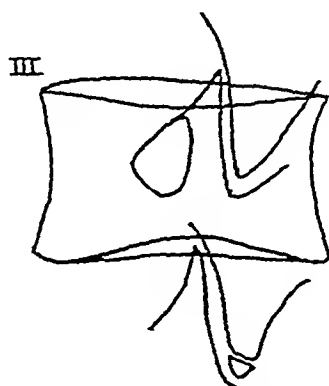


Fig. 6.—Diagram of the roentgenographic findings in case 2, right oblique view.

was no fracture but that the claimant had a congenital lesion of the spine. We therefore decided to give the patient the benefit of the doubt and reported the finding as ununited fractures of the lower articular processes of the third lumbar vertebra. We were not convinced, however, that we were dealing with fractures, but conceded that this may

have been another case of accessory articular processes, as described by Rendich and Westing. The case is therefore reported with the hope that it will stimulate further study of the problem. Rendich and Westing suggested that roentgenographs of the spine of applicants for hazardous positions in industry would prevent the physician's predicament in many doubtful cases of this sort.

After this report was prepared, one of us (W. K. K.) had the opportunity of seeing another case of formation of a gap through a lower articular process.

CASE 2.—J. L. R., aged 41, was being treated for a left ureteral stricture. Pyelographic examination was made on June 13, 1933. Except for slight hydronephrosis on the left side, the pyelograms did not show abnormalities. The roentgenograms, however, revealed a defect in the right lower articular process of the third lumbar vertebra. The gap was not transverse, as in the case reported earlier, but slightly oblique. The smaller fragment showed no atrophy or displacement. The edges of the bone at the gap were slightly denser than the rest of the bone. The spine was straight and did not show other anomalies. Another radiograph, taken according to Rendich and Westing's suggestion, with the patient rotated 45 degrees on the right side, plainly showed the small fragment of bone below the right lower articular process of the third lumbar vertebra. The patient could not remember having received an injury to the back or to any other part of the body. On specific questioning he did not complain of pain or discomfort. There was no limitation of motion in the spine.

Whereas there could be doubt in the first case as to whether we were dealing with a congenital malformation or with the result of an injury, there can be no doubt in the second case that we were confronted with a true case of an accessory articular process of the third lumbar vertebra.

#### SUMMARY

Two cases of formation of a gap through the lower articular processes of the third lumbar vertebra are reported.

In the first case there was a history of possible injury to the spine; therefore a question could be raised as to the correctness of the diagnosis.

In the second case there was no history of trauma, and there were no local symptoms; therefore the case is considered to be one of an accessory articular process of the third lumbar vertebra.

# PERIPHERAL ARTERIAL THROMBOSIS

## SECONDARY TO GONORRHEAL ARTHRITIS AND INTRAMUSCULAR INJECTION OF MILK

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AND

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MINNEAPOLIS

Primary arterial thrombosis of nonembolic origin has been stated<sup>1</sup> to be unquestionably of bacterial origin. Only within the past thirty years, however, has much attention been directed toward, or any observation made of, thrombosis associated with infectious fevers. Arterial thrombosis is not considered to be unusual in cases of influenza, but in the other infectious diseases in which it has been encountered it is described as an uncommon complication. Welch<sup>2</sup> stated that arterial thrombosis associated with gonorrhea is very rare. Heller's<sup>3</sup> collection of only twenty-six instances from the literature illustrates its infrequency of occurrence.

Frazier<sup>1</sup> stated that chemical changes in the blood resulting in a liberation of fibrin ferment must be considered as an important etiologic factor in the production of arterial thrombosis. Welch stated that this factor is of undoubted importance, especially in thrombosis in toxic conditions. It is entirely conceivable that the intramuscular injection of milk or other foreign protein may act on the vascular system as a chemical etiologic factor. We failed, however, to find any record of intramuscular injection of milk resulting in peripheral arterial thrombosis.

Furthermore, it was stated<sup>1</sup> that there have been only a few cases of arterial thrombosis limited to, or terminating in, gangrene of the toes, although it is generally conceded that this lesion is more common in the lower than in the upper extremities. Associated gonorrhea and intramuscular injections of milk as unusual infectious and chemical etiologic

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1. Frazier, C. H.: Thrombosis and Embolism, in Keen, W. W.: *Surgery, Its Principles and Practice*, Philadelphia, W. B. Saunders Company, 1916, vol. 1, p. 433.

2. Welch, W. H.: Thrombosis, in Allbutt, C., and Rolleston, H. D.: *A System of Medicine*, New York, The Macmillan Company, 1909, vol. 6, p. 691.

3. Heller, J.: Ueber Phlebitis gonorrhoeica. *Berl. klin. Wchnschr.* 41:609, 1904.



factors in the production of peripheral arterial thrombotic gangrene, as well as the uncommon location of the resulting lesions, have been considered as justification for the report of the following case.

#### REPORT OF A CASE

The case is that of a white girl, 19 years of age, who was admitted to the Minneapolis General Hospital on Feb. 18, 1931, and discharged on June 8.

*History.*—The patient stated, on admission to the medical service, that five days previously malaise, chills and fever had suddenly developed. The onset of these symptoms was associated with a beginning menstrual period. One day later she noticed pain in the lower abdominal region and stiffness in both wrists and both knees. During the next three days the pain and stiffness spread to the back, ankles and left elbow. She was advised by her family physician to enter the hospital at this time.

The patient had contracted gonorrhea three years before the onset of the illness, and shortly afterward she had suffered from a mild attack of pelvic inflammatory disease. Vaginal smears had been positive for gonococci at that time. Treatment had been received until the smears were repeatedly negative.

*Physical Examination.*—Positive physical findings were limited to the abdomen, extremities and pelvis. Examination of the abdomen showed marked tenderness on palpation over both lower quadrants. No rebound tenderness was present. Moderate tenderness was present about the left elbow and knee, and there was marked tenderness about both ankles. There seemed to be some local heat in these regions, but neither swelling nor redness was noted. Pelvic examination showed a moderate fixation of the uterus and adnexa, with extreme tenderness on palpation or movement of these structures. Pelvic examination also intensified the diffuse pain in the lower abdominal region. The temperature ranged about 101 F., and the pulse rate was 95 beats per minute.

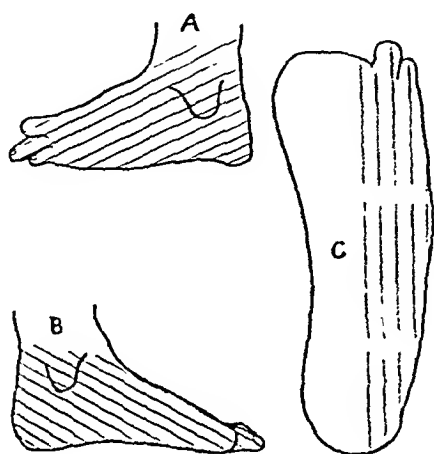
*Laboratory Data.*—The urine was normal. The blood showed 81 per cent hemoglobin and a white cell count of 15,700, 71 per cent of which were polymorphonuclear neutrophils. Repeated vaginal smears were negative for gonococci.

*Diagnosis.*—The clinical impressions were based on the past and present histories and the physical findings. It was concluded that the patient was suffering from gonorrheal arthritis of the left elbow, left knee and both ankles and chronic bilateral gonorrheal salpingitis.

*Therapy.*—The initial medical therapy consisted in the intramuscular injection of 60 cc. of defibrinated blood and the administration of salicylates in doses as large as the patient could tolerate. The symptoms remained unchanged, however, and the temperature continued to range about 101 F. Consequently, 8 cc. of milk was given intramuscularly on the suggestion of a dermatologic consultant. The temperature rose to 105 F.; the pulse became rapid, and the patient complained of great abdominal pain almost immediately after the injection of the foreign protein. Examination of the abdomen showed marked tenderness on palpation in both lower quadrants and definite rebound tenderness. Profuse perspiration, headache, backache, increased pain in the affected joints and leukocytosis were also noted. Swelling, redness, tenderness and local heat were noted in both lips and the left labium majus and on the dorsum of the left foot six days following the injection of milk. The latter symptoms rapidly disappeared, excepting in the left foot, where they subsided gradually. The tissues about the first, second and third toes then

became cold and numb. Later the foot became cold and cyanotic, and beginning gangrene was noted in the toes initially affected. There was now considerable pain in the foot and ankle. The gangrene became well demarcated at a much later date and involved only the first, second and third toes. There was associated superficial anesthesia over the dorsum of the foot to the level of the malleoli and along the lateral half of the sole. The patient was transferred to the surgical service on the development of well demarcated gangrene, and the toes involved were amputated.

*Postoperative Course.*—The patient's septic type of temperature had been slowly subsiding immediately preceding the amputation of the gangrenous toes. The temperature returned to normal following the operative procedure, and the patient was soon discharged from the hospital. The operative wounds healed satisfactorily, and the patient's general condition was much improved, but the areas of



A sketch illustrating the areas of superficial anesthesia on the left foot. *A* indicates the anesthetic area on the dorsum and the lateral aspect; *B*, the anesthetic area on the medial aspect, and *C*, the anesthetic areas on the sole.

superficial anesthesia persisted. The figure illustrates the areas of superficial anesthesia present at the time of discharge. The patient left the city shortly after discharge, and we were unable to follow the subsequent course.

#### COMMENT

The pathogenesis of thrombi is usually described as consisting of four factors: the presence of infective organisms, structural alterations of the intima, disturbances of the blood current and chemical changes in the blood.

It is with the infectious thrombi that the surgeon has to deal most frequently. The infectious diseases with which arterial thrombosis has previously been associated are influenza, typhoid fever, enteric fever, pneumonia, scarlet fever, typhus fever, tuberculosis, variola and the like. Streptococci have been the most frequently encountered offending

organisms. Singer,<sup>4</sup> however, considered the gonococcus as a possible etiologic factor as early as 1898, and the collected cases of Heller<sup>3</sup> substantiated his consideration. The case herein described would seem to be attributed to gonorrhea. However, this conclusion is based largely on circumstantial evidence, as positive findings of the gonococcus were not recorded from pelvic examination or examination of the blood stream or the affected joints during the patient's stay in the hospital. Some credence must be placed, however, on the fact that the patient had a positive smear for gonococci from the genital tract a short time previously; that pelvic examination showed an inflammatory disease process, and that the patient presented, in the minds of the attending internists, a clinical picture of gonorrheal arthritis. It is regrettable that no culture was made from the thrombi at the time of operation, but a negative result would not have eliminated gonorrhea as an etiologic factor, for in most cases bacteriologic examination of such thrombi has yielded negative results.

Structural alterations of the intima of the affected blood vessels as a result of the infectious disease may have been an etiologic factor. The action of infective agents in the causation of focal and diffuse diseases of the arteries has received considerable attention. The occurrence of acute and chronic arteritis as a result of various infective diseases, such as acute articular rheumatism, enteric fever, typhus fever, variola, scarlet fever, pneumonia, endocarditis, septicemia, syphilis, tuberculosis and leprosy is well established,<sup>2</sup> and it is not unreasonable to conclude that arterial thrombosis following gonorrhea may be referable to an infective arteritis. Other common causes of intimal changes would be unlikely in such localized areas of the vascular system and in a patient of this age.

Retardation of the blood current is but a predisposing or contributory cause, and consequently is of significance only when associated with a lesion of the vascular wall, the presence of organisms or chemical changes in the blood. The circulation in the lower extremities is relatively sluggish, and with evidence of an infectious process and possible chemical changes in the blood this factor may well have been contributory in the production of the lesions described.

That chemical changes in the blood are an etiologic factor in the production of such thrombi is as yet somewhat hypothetical. It is generally accepted that the use of foreign protein therapy is sound and productive of good results in many cases of gonorrheal arthritis and pelvic inflammatory disease. Schulman<sup>5</sup> enthusiastically recommended the intramuscular injection of milk as giving the most brilliant results in gonor-

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4. Singer: Thrombose und Embolie im Wochenbett mit besonderer Berücksichtigung der gonorrhoeischen Infection, *Arch. f. Gynäk.* 56:218, 1898.

5. Schulman, M.: Parenteral Protein Treatment of Arthritis, with Special Reference to Milk Injections; Its Relation to Anaphylaxis, *M. Rec.* 98:47, 1920.

rethral arthritis. Murray<sup>6</sup> stated that the great majority of workers have adopted sterile cow's milk as the agent of choice in the use of foreign protein therapy for pelvic inflammatory disease.

Neuhof and Hirschfield<sup>7</sup> showed, however, that the intravenous and intramuscular injection of sodium citrate, which is generally known as an anticoagulant, results in prompt and pronounced shortening of the coagulation and bleeding time. Salomon and Vey<sup>8</sup> also showed experimentally that the intravenous and intramuscular injection of various proteins and chemical agents results in a definitely decreased coagulation time. Conversely, Goldenberg and Panisset<sup>9</sup> injected milk intravenously into rabbits and mice, with no ill effects of any kind. The impression exists, however, that the reaction to many foreign proteins and chemicals injected intramuscularly is an increase in the coagulating power of the blood.

The reaction of the patient herein described to the injection of foreign protein was in no way unusual, the high temperature, leukocytosis, profuse perspiration, headache, backache, abdominal pain and increased pain in the affected joints being common immediate sequelae of this treatment. It is not difficult, however, to associate a possible chemical action on the blood with the other etiologic factors in the production of arterial thrombosis. At least the injection of milk was a potential etiologic factor in this case and clinically seemed to exert a potent influence in the production of the thrombotic lesions described.

#### SUMMARY

1. A case is reported in which a gonorrheal infectious process and the intramuscular injection of milk seem to be etiologic factors in the production of peripheral arterial thrombosis and gangrene in an unusual location.
2. Arterial thrombosis with resulting gangrene limited to the toes is a very uncommon occurrence.
3. Gonorrheal arthritis as an infectious etiologic factor in the production of arterial thrombosis is rare.
4. We failed to find a previous record of the intramuscular injection of milk as a probable etiologic factor in the production of peripheral arterial thrombosis.

6. Murray, P. M.: Milk Injection in Pelvis Infection. *Am. J. Surg.* 8:570, 1930.

7. Neuhof, H., and Hirschfeld, S.: The Intramuscular Administration of Sodium Citrate, a New Method for the Control of Bleeding. *Ann. Surg.* 76:1, 1922.

8. Salomon, R., and Vey, E.: Der Einfluss von Proteinkörpern auf die Blutgerinnung. *Arch. f. Gynäk.* 116:317, 1922.

9. Goldenberg, L., and Panisset, L.: Parenteral Injections of Milk, *Paris méd.* 2:450 (Nov. 29) 1924.

# INFLUENCE OF VENOUS STASIS ON HETEROTOPIC FORMATION OF BONE

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AND

PAUL E. McMASTER, M.D.

LOS ANGELES

The question of the influence of circulatory changes on the healing of bone has been discussed by many authors with conflicting opinions. Pearse and Morton<sup>1</sup> and McMaster and Roome<sup>2</sup> have offered experimental evidence that the healing of defects of bones is accelerated by venous stasis. On the other hand, sympathectomy, with its increased flow of blood in the extremity, has been empirically advocated in the treatment of fractures by Leriche,<sup>3</sup> Colp and Mage<sup>4</sup> and others. Pearse and Morton,<sup>5</sup> Key and Moore<sup>6</sup> and McMaster and Roome<sup>2</sup> found no experimental confirmation of the value of such therapy. Clinically, certain atrophies of bone are explainable on the basis of arterial hyperemia (Greig<sup>7</sup>). Harris<sup>8</sup> listed several conditions known to cause hypertrophy and lengthening of the bones of children in which various degrees of venous stasis exist.

Formation of bone may be initiated by the transplantation of certain epitheliums into certain connective tissues. This effect was studied extensively by Huggins,<sup>9</sup> who found that bone occurred nearly con-

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From the Department of Surgery, the University of Chicago.

1. Pearse, H. E., and Morton, J. J.: The Stimulation of Bone Growth by Venous Stasis, *J. Bone & Joint Surg.* **12**:97, 1930.

2. McMaster, P. E., and Roome, N. W.: The Effect of Sympathectomy and of Venous Stasis on Bone Repair, *J. Bone & Joint Surg.* **16**:365, 1934.

3. Leriche, R.: Indications et resultats de la sympathectomie périartérielle dans la chirurgie des membres, *Congres Français de Chirurgie*, Paris, 1927, p. 435.

4. Colp, R., and Mage, S.: Experiences with Periarterial Sympathectomy in Fractures of the Lower Extremity, *J. A. M. A.* **97**:1069 (Oct. 10) 1931.

5. Pearse, H. E., and Morton, J. J.: The Influence of Alterations of the Circulation on the Repair of Bone, *J. Bone & Joint Surg.* **13**:68, 1931.

6. Key, J. A., and Moore, R. M.: Healing of Fractures, of Defects in Bone and of Defects in Cartilage After Sympathectomy, *Arch. Surg.* **26**:272 (Feb.) 1933.

7. Greig, D. M.: Clinical Observations on the Surgical Pathology of Bone, Edinburgh, Oliver & Boyd, 1931, p. 227.

8. Harris, R. I.: The Effect of Lumbar Sympathectomy on the Growth of Legs Shortened from Anterior Poliomyelitis, *J. Bone & Joint Surg.* **12**:859, 1930.

9. Huggins, C. B.: The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377 (March) 1931.

stantly in dogs on autotransplantation of the mucosa of the urinary bladder to the parietal fascias or muscles. A cyst forms by proliferation of the mucosa, and bone appears in relation to the newly formed mucous membrane from eleven to eighteen days after the transplantation (fig. 1). The experiments to be described are a study of the effects of venous stasis on such heterotopic deposits of bone.



Fig. 1.—Photomicrograph of bone formed by transplantation of mucosa of the urinary bladder into muscle planes;  $\times 110$ . Note the bladder mucosa at *A* and the undecalcified bone at *B*.

#### EXPERIMENTAL METHODS

In each of six dogs, under morphine-ether anesthesia and with aseptic precautions, a small portion of the dome of the urinary bladder was excised and the defect closed. The mucosa was carefully dissected from the fragment, and two pieces, usually about 5 by 5 mm., of as nearly identical size and shape as possible, were sutured to the muscles of both hind legs beneath the deep fascia by fine inter-

rupted silk sutures. The right femoral vein and its four or five tributaries (saphenous, lateral circumflex, anterior femoral and muscular veins) in the upper part of the thigh were doubly ligated and portions excised. Roentgen studies were made at intervals. No suppuration occurred in any of the wounds, and no impairment of motion of the legs was noted. Five dogs died or were killed from twenty to three hundred and fifty days postoperatively; in three of these the cysts of the bladder mucosa and adjacent bone were excised en masse, the soft parts dissolved by boiling in a 1 per cent solution of sodium hydroxide for from thirty to sixty minutes, and the plaques of bone washed, dried and weighed. Dog 989 was kept, and the density of the transplant bone observed at intervals by means of roentgenograms for more than two and a half years.

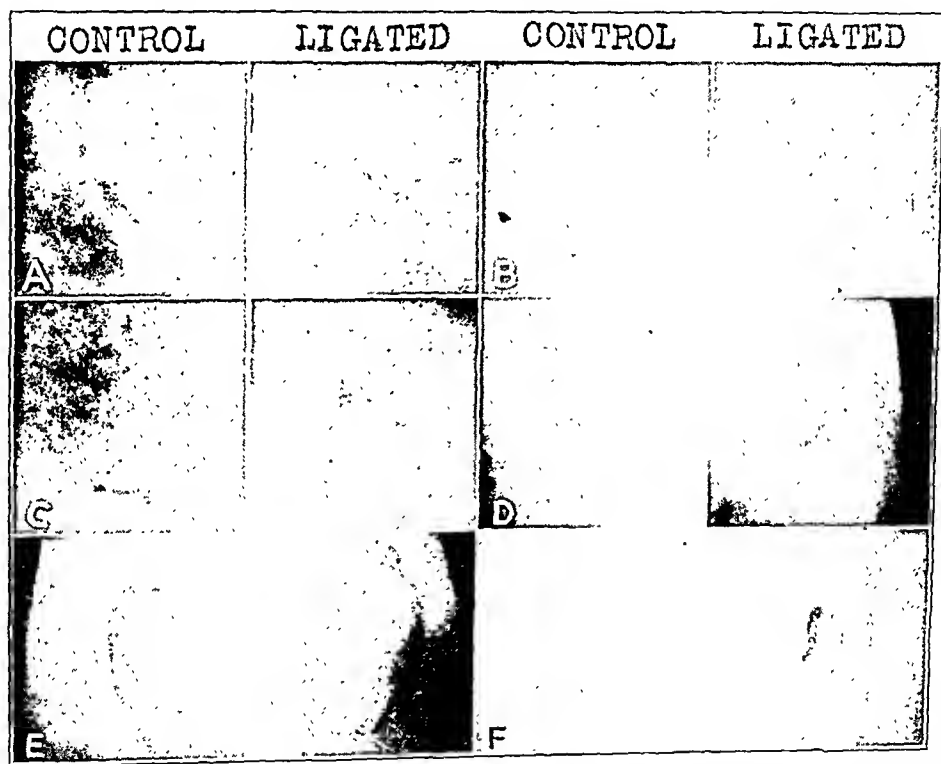


Fig. 2.—Roentgenograms showing the bone resulting from the mucosa transplantation of the bladder into the muscles of the leg: A, dog 173; B, dog 175; C, dog 283; D, dog 291; E, dog 927; F, dog 989. Note that in all films more dense bone is present on the side with venous ligations.

#### RESULTS OF EXPERIMENTS

By means of the roentgenograms, more dense formation of bone was observed in the leg with the ligated veins in five of the six animals (fig. 2). In one case (175) it was doubtful if there was any difference between the two sides in many of the roentgenograms.

In the cases in which the density of the bone was followed by roentgenograms over a long period, there was an increase in density for from one and a half to five and a half months, then a stationary

period followed by well marked diminution of the density of the bone, from four and a half to seven months postoperatively. Traces of bone persisted longer than two and a half years in the one dog studied over that period (fig. 3).

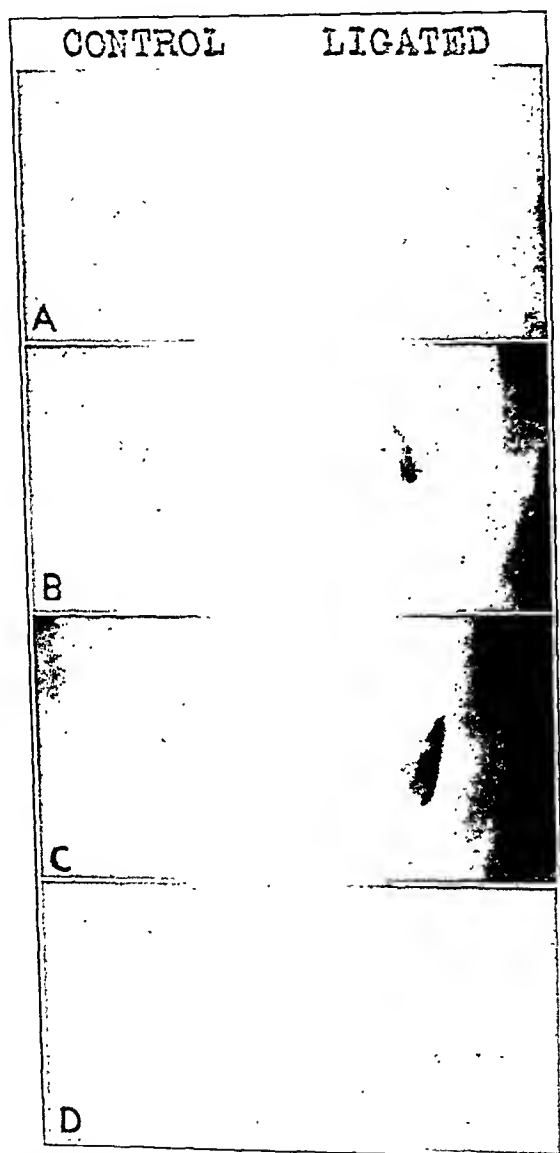


Fig. 3 (dog 989).—Roentgenogram of transplanted bone at intervals, showing appearance at (A) twenty-one days, (B) thirty-five days, (C) one hundred and forty-five days and (D) four hundred and thirty-three days. Note the progressive increase in the density of the bone in the three upper films and the decreased density in the last film.



At necropsy on three of the animals (927, 173 and 175) there was definitely more bone recoverable from the ligated side in two cases and equal amounts in one case. The weights of bone obtained were as follows: dog 927, ligated leg, 157 mg., and control leg, 103 mg.; dog 173, ligated leg, 23 mg., and control leg, 1 mg.; dog 175, ligated leg, 21 mg., and control leg, 21 mg.

#### COMMENT

In spite of the obvious technical difficulty of transplanting exactly equal pieces of mucosa of the bladder into the legs of the dogs, it is thought that the consistent results obtained are significant, and that heterotopic formation of bone is accelerated by venous stasis. This conclusion is probably applicable to the general problem of the healing of defects of bone and fractures; i. e., that venous stasis promotes osteogenesis.

It is noteworthy that the bone formed in the soft parts by transplantation of mucosa of the bladder increases in density for a period, and then gradually atrophies. It thus behaves similarly to adult bone transplanted into the soft parts, as described by Phemister.<sup>10</sup> Traces of bone persisted longer than two and a half years, however, in the one dog studied over that period; the presence of the mucous membrane may be a factor in causing its persistence in the absence of stress and strain.

#### SUMMARY AND CONCLUSIONS

The effect of venous stasis on heterotopic formation of bone induced by transplanting similar portions of mucosa of the urinary bladder into the muscle planes of both hind legs, was studied in a series of six dogs. The femoral vein and its tributaries in the upper portion of the thigh were ligated and excised on one side, while the other leg was used as a control. It was found (1) that in five cases more bone was formed in the leg with venous ligations than in the control leg, while in one case the amounts were equal, as studied by roentgenograms and by weighing the bone plaques; and (2) that the bone formed about the transplant increased in density for a period of a few months, then atrophied, although the bone did not entirely disappear from the legs in the one case studied for two and a half years.

It was concluded that heterotopic formation of bone is accelerated by venous stasis.

5728 Drexel Avenue.

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10. Phemister, D. B.: The Fate of Transplanted Bone and Regenerative Power of Its Various Constituents, *Surg., Gynec. & Obst.* 19:303, 1914.

# SUBCUTANEOUS BILATERAL SARCOID OF THE GLUTEAL REGION

REPORT OF A CASE

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Among the many phenomena associated with arthritis and rheumatoid conditions nodular involvements of the skin compose an interesting group. Frequently some of the nodules resemble those seen in other conditions, so that the appearance of such masses is not always conclusive proof of a rheumatic etiology. Therefore, a careful differential diagnosis is essential.

## REPORT OF CASE

*History.*—On March 14, 1932, a Jewish woman, aged 50, presented herself at Dr. Finkelstein's clinic. Four weeks before, while bathing, she discovered four lumps over the buttocks. The lumps were hard, painless and somewhat movable.

In 1928 a falling piece of ceiling struck the patient on the head. Examination at that time failed to reveal any injury. The pain disappeared after the application of an ice-bag. In 1929 she complained of a chronic cough and nervousness. At that time a few dry râles were heard in both lungs. Her blood pressure was 160 systolic and 100 diastolic, the urinalysis gave negative results and degeneration of the myocardium was diagnosed. Varicose veins were found, and for these she received four injections into the veins of the left leg, three of invert sugar and sodium chloride and one of sodium salicylate and sodium chloride. A severe reaction followed the last injection. The patient had two children and had had no miscarriages. The menopause set in at 42 years of age. With the exception of chronic constipation, she had had no other illnesses.

The husband had a right orchotomy for tuberculous epididymitis and at the time of his wife's examination was under treatment for a peripheral circulatory disturbance. The family history was otherwise irrelevant.

*Examination.*—The patient weighed 170 pounds (77.1 Kg.), was 5 feet 4 inches (162.6 cm.) tall, was somewhat pale and had false teeth. The throat and tonsils appeared normal. The internal organs gave no indication of a pathologic process. At the level of the third sacral vertebra, 1½ inches (3.77 cm.) from the midline, hard nodules could be palpated bilaterally which measured from 1 to 2 inches (2.5 to 5 cm.) in diameter. Two smaller lumps, each the size of a bean, were situated about 3 inches (about 7.5 cm.) from the midline. The masses were in the

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Read before the Clinical Society of the Hospital for Joint Diseases, April 12, 1933.

subcutaneous tissue (fig. 1). The overlying skin was somewhat roughened. A Wassermann test was negative. A quantitative tuberculin test and a complement-fixation test for gonorrhea were negative; a sedimentation test was read as 17 per cent. A roentgenogram of both lungs showed a calcified nodule in the upper lobe of the left lung.

*Biopsy.*—On March 24, 1932, a specimen was removed for biopsy. Under procaine hydrochloride anesthesia, a slightly curved incision 3 inches (7.5 cm.) long was made over the left lower part of the back, along the upper fibers of the gluteus maximus muscle. On retracting the skin, a hard fibrous tumor, irregular in outline and infiltrative, was seen extending along the fascial plane, in places into the skin and in others toward the muscle. On attempting to excise the mass, a large number of vessels were encountered. A tumor about the size of a plum was removed and sent to the laboratory.

The microscopic examination was made by Dr. H. L. Jaffe, director of the laboratory, whose report follows: "Sections show very extensive single and conglomerate tubercles. There is no caseous necrosis. There is an extensive interstitial reaction in association with the inflammatory process. Tubercle bacilli will

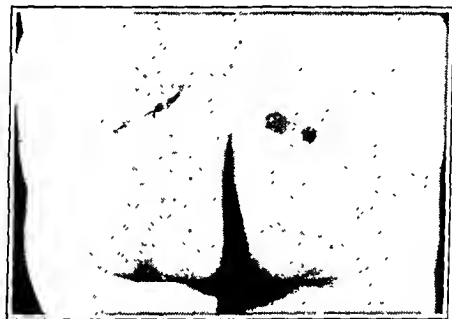


Fig. 1.—On the left side the scar left following the biopsy can be seen, and on the right, ink markings indicating the nodules remaining.

be searched for in the section. I would suggest inoculating some of the material into a guinea-pig. The appearances are all in favor of the lesion being tuberculous. The exceptional possibility of its being syphilitic must be considered" (figs. 2 and 3).

*Course.*—The patient was discharged from the hospital on March 26. She came back to the clinic for dressings. On March 30, she complained of bleeding from the wound. A superficial slough developed, and the patient was readmitted to the hospital on April 4. The stitches were removed and a boric acid dressing was applied to the wound. Our diagnosis of possible sarcoid was then confirmed by Dr. Peck. The culture for tubercle bacilli and inoculation of guinea-pigs with secretion of the wound and tumor gave negative results. Sections stained for tubercle bacilli revealed none. Amyloid was absent on examination of specially stained sections made at the request of Dr. Gross, who also found in the nodules a resemblance to foreign body tumors. The wound healed under the dressings. The patient was discharged on April 13, but continued to receive injections of sodium cacodylate twice a week. Under this treatment the nodules on the right side diminished, until after eighteen injections, they were completely absorbed. The treatment was discontinued on July 6.

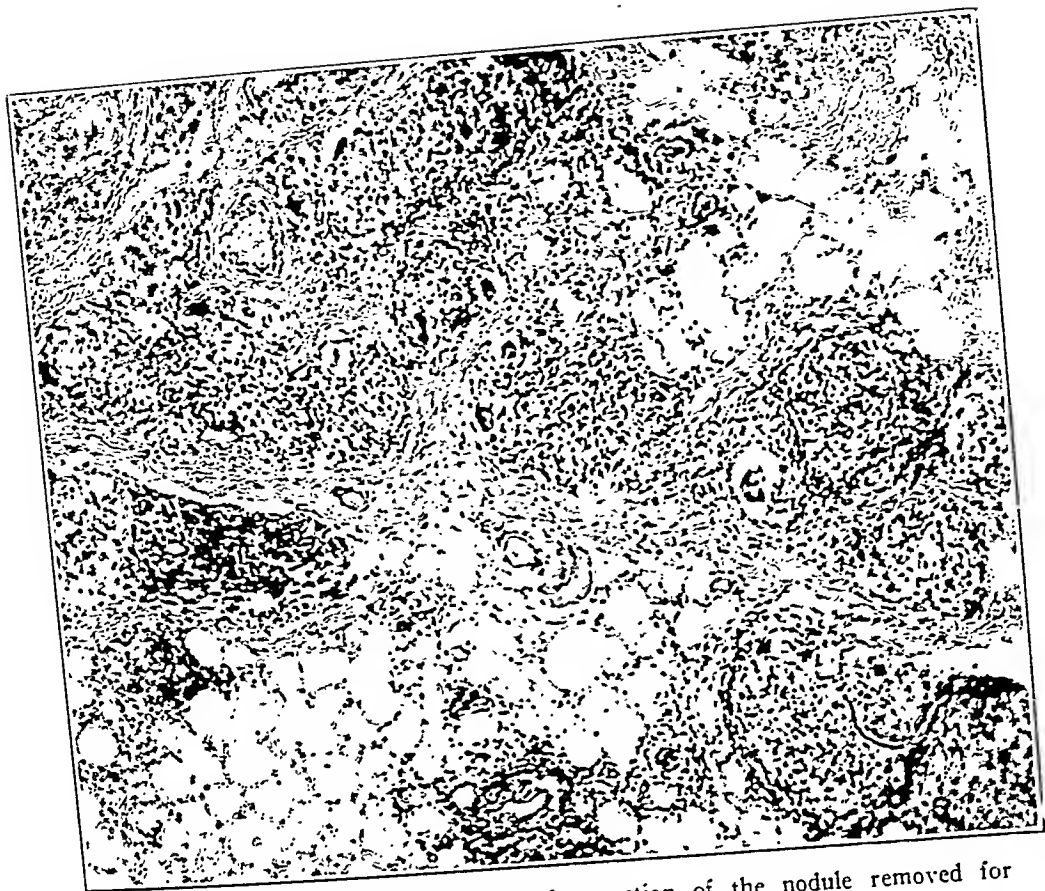


Fig. 2.—Low power magnification of a section of the nodule removed for biopsy, showing tubercles with giant cells divided off from one another by septums of connective tissue and numerous lymphocytes.

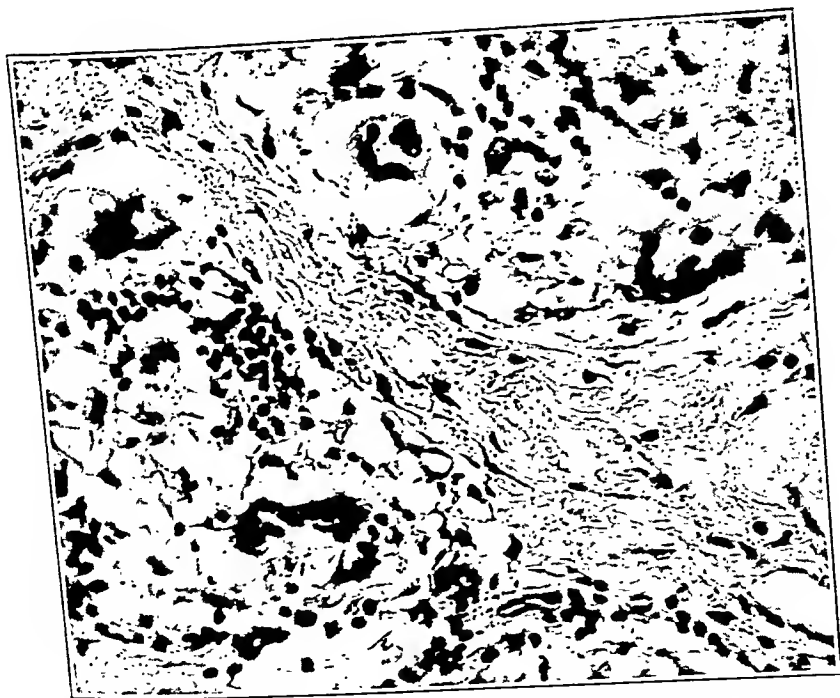


Fig. 3.—High power magnification of a section of a tubercle showing giant cells.

*Reexamination.*—On Jan. 23, 1933, a review of the patient's condition showed a firm scar in the left gluteal region. All the nodules had been absorbed completely. A slight amount of atrophy of the overlying skin and brownish pigmentation were still present.

After Boeck<sup>1</sup> in 1899 designated the name "sarcoid" for certain tumors, Fendt<sup>2</sup> defined it as signifying a circumscribed benign tumor of limited growth composed of groups of round cells, divided off in its substance by septums, but as a whole encapsulated and frequently healing in response to treatment with arsenic. Many examples of the condition were found and described, but it was not until 1910 that Darier<sup>3</sup> brought forth the first comprehensive and satisfying classification.

He grouped all cases into four sections: (1) multiple benign sarcoid of Boeck; (2) subcutaneous type, of Darier-Roussy;<sup>4</sup> (3) erythema induratum of the extremities; (4) Spiegler-Fendt<sup>5</sup> type, a nontuberculous nodule composed of round cells, resembling the condition known as leukemia cutis or lymphodermia.

The case described here belongs to the Darier-Roussy group. Generally speaking, tumors in this group are subcutaneous, round or oval, the size of a walnut and painless. They occur on the trunk, especially on the upper part, or on the side of the abdomen. They seldom ulcerate, and there is usually a negative reaction to tuberculin. Histologically the nodules are composed of epithelioid and giant cells, mostly of the sarcoma type, although occasionally of the true Langhans type with lymphatic infiltration about the epithelioid layer. The nodules may occur in chains along the blood vessels.

Kuznitsky<sup>6</sup> described cases in which the cutaneous manifestations were coupled with a similar involvement of the internal organs, including the liver, spleen, lungs, lymph glands and kidneys. He considered the disease systemic rather than cutaneous.

A number of conditions must be differentiated from sarcoid, including among others myogelosis, subcutaneous rheumatic nodules, tuberculosis cutis, gumma, metastatic tumors, inflammatory reactions around sites of injections and aberrant glands.

Etiologically, sarcoid has been much in doubt, Boeck claiming it to be tuberculous, Pautrier<sup>7</sup> syphilitic and others infectious but of unde-

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1. Boeck: *J. Cutan. Dis.* **17**:543, 1899.

2. Fendt: *Arch. f. Dermat. u. Syph.* **53**:213, 1900.

3. Darier: *Monatsh. f. prakt. Dermat.* **50**:419, 1910.

4. Darier and Roussy: *Ann. de dermat. et syph.* **5**:144, 1904.

5. Spiegler: *Arch. f. Dermat. u. Syph.* **27**:163, 1894.

6. Kuznitsky: *München. med. Wchnschr.* **62**:1349, 1915.

7. Stillians, A. W.: *J. A. M. A.* **77**:1615 (Nov. 19) 1921.

terminated cause. Kyrle<sup>8</sup> found tubercle bacilli in the lesions as early as ten days after their onset, yet was not able to demonstrate them in specimens from the same lesion at thirty-six days, while Pautrier found syphilis associated with sarcoid of the Boeck type and also with that of the Darier-Roussy type. In the exceptional cases observed by Pautrier, cure was accomplished by antisyphilitic treatment. Thereafter he was of the belief that the condition was as closely related to syphilis as to tuberculosis. Stillians,<sup>7</sup> in 1921, concluded as a result of his work on the subject that neither of the two types so treated by Pautrier was ever caused by *Spirochaeta pallida*, but that the erythema induratum type may sometimes be so caused.

Prognosis in cases of sarcoid must be guarded as to the disappearance of the nodules, but may be good as to survival.

The treatment, in addition to that mentioned, has in some cases included use of endothermy, mercurous chloride, tuberculin and roentgen rays. Atrophy and slight pigmentation usually follow the absorption and disappearance of the nodules.

#### SUMMARY

A subcutaneous tumor of the physical attributes seen in this case, not associated with rheumatic involvements, associated with negative reactions to the Wassermann test and to the various tests employed with and diagnostic of tuberculosis, uncomplicated by any phenomenon of metastasis, not involving the general health, shown by biopsy to have a definite and characteristic histologic structure, not ulcerating and responding typically to arsenical medication, can by these criteria be safely designated as a true sarcoid tumor of the Darier-Roussy type.

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8. Kyrle, J.: Arch. f. Dermat. u. Syph. 131:33, 1921.

# INFLUENCE OF BLADDER TRANSPLANTS ON THE HEALING OF DEFECTS OF BONE

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Having been interested in the problem of osteogenesis and the healing of bone we were attracted by the work of Huggins,<sup>1</sup> who showed that if the mucous membrane of the bladder was transplanted to the subcutaneous tissue of dogs the transplant tended to produce a cyst lined by bladder epithelium, and true bone tended to be formed in the wall of the cyst. It occurred to us that epithelium from the bladder might stimulate osteogenesis in defects in bone and cause union to occur in defects which would normally result in nonunion. In this article we report experiments in which relatively large defects in bone in the ulnas of dogs were bridged by transplants of the mucous membrane of the bladder of the same animal.

## REVIEW OF THE LITERATURE

The literature on heteroplastic formation of bone and especially on formation of bone in the genito-urinary tract has been reviewed by Huggins,<sup>1</sup> so that it will not be necessary to repeat it here. Neuhof<sup>2</sup> noted that if fascia was transplanted into defects in the urinary bladders of dogs, bone constantly developed on the surface of the fascia which was adjacent to the bladder cavity, and that the bone was invariably confined to the transplanted fascia. He believed that the bone was formed by metaplasia of the tissue and that the metaplasia was caused by the deposition of lime salts in the necrotic tissue of the fascial patch which was in contact with the urine. It was his belief that the imbibition of calcium salts acted as a stimulus to the surrounding connective tissue which caused it to build up as powerful a barrier as possible, namely, bone.

Neuhof's experiment was repeated, and the observation on the formation of bone was confirmed by Phemister.<sup>3</sup> Phemister noted that while

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From the Department of Surgery, Washington University Medical School.

1. Huggins, C. B.: The Formation of Bone under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377 (March) 1931.

2. Neuhof, H.: Fascia Transplantation and the Visceral Defects, *Surg., Gynec. & Obst.* **24**:383, 1917.

3. Phemister, D. B.: Ossification in Kidney Stones Attached to the Renal Pelvis, *Ann. Surg.* **78**:239, 1923.

bone was formed in the fascial patch in the dog, it was not formed in similar transplants in the bladders of rabbits and sheep. He believed that this was due to the fact that in dogs the urine is acid in reaction while in herbivorous animals it is alkaline, and he believed that the acid reaction had something to do with the formation of bone.

Huggins<sup>1</sup> transplanted mucous membrane from the bladder into various tissues, and showed that if a strip of the mucous membrane of the bladder was transplanted to the rectus sheath, fascia lata, subcutaneous tissues or muscle of the dog, true bone developed in the transplant and that this bone contained haversian canals and hematopoietic marrow. The bone was always produced in the wall of the cyst and appeared to be formed under the influence of the proliferating cells lining the cyst. Huggins and Compere<sup>2</sup> showed that in the majority of instances the fluid contained in these cysts was unusually high in calcium and phosphorus as compared with the blood of the same animal. This capacity to stimulate formation of bone was apparently specific for the bladder since bone did not occur in transplants of other epithelial tissues (from the gallbladder or gastric, jejunal and prostatic epithelium). Furthermore, the bladder transplants seemed to require a certain type of fibrous tissue for formation of bone, as no bone was formed when bladder mucosa was transplanted into the kidney, liver or spleen.

#### MATERIALS AND METHOD

This report is based on the results obtained from operations on twenty-four adult dogs. The operative procedure was as follows:

Under ether anesthesia the hair was removed from the abdomen and forelegs. The skin was prepared for operation with iodine. The urinary bladder was exposed and a piece of the wall of the bladder, approximately 2 cm. square, was excised. The defect in the bladder was sutured, and the abdominal wound was closed. The mucous membrane from the bladder was then dissected from the muscularis and was divided into two equal portions. The lower third of the ulna of each leg was exposed, and approximately 1 cm. of the shaft was resected subperiosteally. Such a large defect will usually result in nonunion. On the right side, one of the pieces of mucous membrane from the bladder was sewed into the defect of the ulna, while the left side was kept as a control. The wounds in the two legs were then closed in layers. Through a separate incision in the abdominal wall, the other half of the mucous membrane from the bladder was spread out on the deep fascia of the abdominal wall and was sutured in place, after which the wound was closed. The dogs were killed at intervals of from seven days to nine months. The specimens were examined in the gross; then, after roentgenograms had been made they were fixed, decalcified, sectioned, stained and studied microscopically.

<sup>2</sup> Huggins, C. B., and Compere, E. L.: Calcium and Phosphorus Content of Epithelial Lined Cysts from Transplantation of Mucosa of Urinary Bladder to Rectus Sheath in Dogs. *Proc. Soc. Exper. Biol. & Med.* **27**:753 (May) 1930.



In addition to the experiments just described, ten experiments were performed in which the bladder was opened and some of the epithelium was scraped off the surface. These scrapings were transplanted into defects in the right ulna of the same animal, while a similar defect was made in the left ulna for a control.

## RESULTS

The results of the longer experiments are shown in the table. Union occurred on the control side (left) in only two instances.

In the right leg, in which the defect in the bone was bridged by a strip of bladder mucosa, union by bone occurred nine times; new bone was formed in the defect in every case, and in thirteen of the sixteen experiments the production of bone was marked. Not only was new bone produced in the defect, but union was the rule, and even in cases in

*Results of Transplanting Mucous Membrane from the Bladder to Resected Right Ulnas of Dogs\**

Dog	Time, Days	New Bone		Union		Atrophy	
		Right	Left	Right	Left	Right	Left
355.....	35	+++	0	+	—	—	+
B33.....	49	+++	+	—	—	—	+
B6.....	49	++	—	+	—	—	+
400.....	52	++	—	+	—	—	+
B40.....	57	+++	—	—	—	—	+
B42.....	59	+++	—	+	—	—	+
B54.....	59	++++	—	+	—	—	+
A19.....	60	++++	++	—	—	—	+
B20.....	71	+++	—	—	—	—	+
352.....	73	++++	—	+	—	—	+
S41.....	75	++	—	—	—	—	+
A9.....	90	+++	—	+	—	—	+
B43.....	99	++++	—	+	—	—	+
353.....	217	++++	++++	+	+	—	—
A16.....	270	++++	++++	+	+	—	—
166.....	270	++++	—	+	—	—	+

\* The left ulna is the control.

which union by bone did not occur, the atrophy which was uniformly present in the control experiments (with nonunion) was not present on the side which contained the bladder transplant.

*Gross Appearance.*—In the experiments of short duration there was little difference between the control and the defect which was bridged by the bladder transplant except that the callus tended to be more voluminous and more firm on the side with the transplant. This callus contained cysts which varied in size directly as the duration of the experiment. In experiments of long duration, in which the control sides did not unite by bone, the ends of the fragments were reduced in diameter, were atrophic in appearance, and the defect was bridged by a strand of dense fibrous tissue. In the same animals the ulnar defects which had been bridged by bladder mucosa presented very different pictures. Here the ends of the bones were usually enlarged and rather more dense than normal, and the defect was filled by a mass of tissue

which consisted of either callus or bone and which contained cysts, varying in size directly as the duration of the experiment. In some of the longer experiments these cysts were quite large and projected from the side of the bone, the largest individual cyst, which measured 2 by 1.5 by 1 cm., being produced in the experiment which lasted for two hundred and seventeen days. In practically every instance these cysts were multilocular, or else multiple small cysts were present.

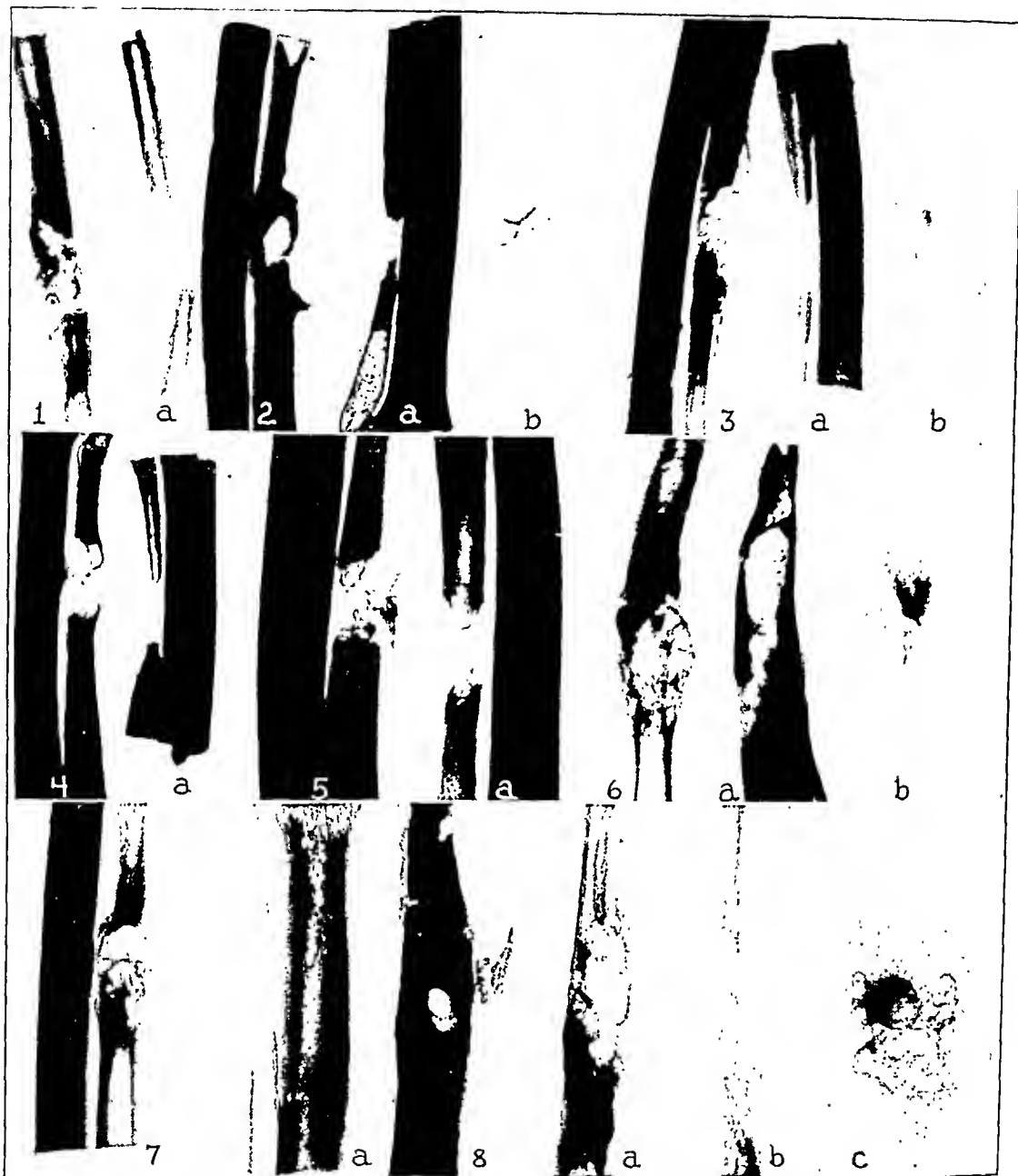
*Roentgen Examination.*—In the seven and fifteen day experiments the roentgenograms of the transplant and control sides were practically the same, but in the experiments which lasted from three to four weeks the roentgenograms showed a thin strand of calcified material stretching between the ends of the bone on the transplant side, while there was no evidence of new bone bridging the defects on the control sides.

In the longer experiments the defects in the control not only showed nonunion, but the bones on the control side exhibited atrophic changes which were definitely present as early as thirty-five days after the operation. These changes consisted not only of a rarefaction of the ends of the bones, but also of a definite decrease in diameter. Although the atrophy occurred more rapidly in some animals than in others, it was progressive, and was most marked at the ends of the fragments. For instance, in one of the forty-nine day experiments the upper fragment of bone was reduced to about half its normal diameter, and tapered down to a thin point. In others the bones maintained approximately their normal diameter for a longer period, but in all of the later experiments the atrophy on the control side was definite. One of the two instances in which union occurred on the control side was an exception, and in this ulna there was little or no demonstrable atrophy (figs. 1 to 8).

The defects which had been bridged by the bladder transplants presented a different appearance, for in all of these in which the experiment lasted over thirty-five days the ends of the fragments retained their normal size and density or were unusually large and more dense than normal. Not only was there no atrophy, but union by bone occurred in twelve of the sixteen experiments (table and figs. 1, 3, 6, 7 and 8).

In the four instances in which union by bone failed to occur on the side with the transplant, not only was there no atrophy, but considerable new bone was produced in the defect (figs. 2, 4 and 5).

Of the two cases of union on the control side one occurred in the seven month, and the other in a nine month, experiment (figs. 6 and 8). In the seven month experiment the control side showed union, with reestablishment of the medullary cavity (fig. 6). These two experiments also showed the type of union produced by the bladder transplant; that is, the bone became enlarged, the ends of the fragments became



Figs. 1 to 8.—Roentgenograms showing: defects of bone in the ulna bridged by transplants of bladder mucosa; defects in the control in the opposite ulna; four cysts formed by bladder transplants in the abdominal wall. 1. Bladder transplant after thirty-five days; *a*, control. 2. Bladder transplant after fifty-nine days; *a*, control; *b*, cyst in the abdominal wall. Note in figure 2 two spicules of new bone attached to the distal fragment, but not united by bone to the proximal fragment. There is a small stellate mass of bone in the cyst in the abdominal wall. 3. Bladder transplant after fifty-nine days; the defect is bridged by a mass of bone which contains numerous small cysts, causing it to have a worm-eaten appearance; *a*, control; *b*, a cyst in the abdominal wall. 4. Bladder transplant after seventy-five days; the defect is occupied by two large cysts resulting in nonunion; *a*, control. 5. Bladder transplant after seventy-five days; there is nonunion on both sides, but on the side of the bladder transplant there is a considerable amount of new bone attached to the lower fragment, the defect being occupied by cysts; *a*, control. 6. Bladder transplant after two hundred and ten days; *a*, control with union; *b*, cyst in the abdominal wall. 7. Bladder transplant after two hundred and seventy days; note the multiple cysts in the bone bridging the defect on the side with the transplant; *a*, control. 8. Bladder transplant after two hundred and seventy days; note the cavity in the bone on the side of the ulna; *a*, lighter print to show a cyst in the bone; *b*, control, showing union; *c*, cyst in the abdominal wall.

eburnated, and the defect was occupied by a mass of tissue containing bone and many clear areas. These clear areas represented multiple cysts. In addition to the cysts in the bone there were, in these two instances, large cysts projecting from the sides of the bone at the site of the preexisting defect.

A good example of the end-result in the defects in the transplant and control is shown in the specimen from the experiment lasting two hundred and seventy days (fig. 7). Here the multiple cysts possessed a dense fibrous wall on their free surfaces and contained a thin brownish fluid. Occasionally part of the wall of the cyst projecting from the shaft of the ulna contained considerable bone, as illustrated in figure 8.

*Abdominal Transplants.*—All of the abdominal transplants produced cysts which varied in size directly as the duration of the experiment, the smallest appearing in the earlier experiments and the largest, measuring 4.5 by 2.5 cm., occurring in a nine month experiment. All of the cysts contained a thin brownish fluid and all possessed a base of dense connective tissue and a dense fibrous wall, which composed the dome of the cyst. In all except the first two transplants, definite bone was produced, and this bone was always present in the base of dense connective tissue and never in the dome of thin connective tissue.

In the microscopic sections bone was seen in the wall of the abdominal cyst of the twenty-one day experiment. However, in eight of the twenty experiments which lasted thirty-five days and longer, the bone was so small in amount that it was not demonstrated in the roentgenograms of the cysts.

The amount of bone produced in the walls of the abdominal cysts was not as great as the amount of bone produced around similar transplants of mucous membrane from the bladder which were placed across a fresh defect in the ulnas of the same animals (figs. 2, 3, 6 and 8).

*Microscopic Examination.*—Controls: In the controls, the defect in the early experiments was filled with a mass of blood clot and granulation tissue, and there was some proliferation of osteogenic tissue from the ends of the fragments and beneath the periosteum. There was no tendency to form a strip of new bone along the periosteum which bridged the defect. The subperiosteal new bone projected only a short distance beyond the ends of the fragments and tended to dip into the defect and become continuous with the new bone springing from the osteogenic tissue in the medullary cavity, thus forming a sort of end-bulb of callus and new bone. However, instead of the formation of new bone progressing and tending to fill the defect, the process ceased in a short time and the new bone was absorbed, and the defect became filled with fibrous tissue while the ends of the fragments atrophied.

In a specimen examined thirty-five days after the operation the defect on the control side was filled with a mass of fibrous tissue, and the ends of the fragments were markedly atrophied, the atrophy apparently being due to large numbers of osteoclasts eroding the bone at the ends and around the circumference of the fragments beneath the periosteum. This osteoclastic absorption continued throughout the experiments and must sometimes have been present simultaneously with a small amount of formation of new bone, since in most of the controls there was evidence of osteoclastic resorption as well as formation of new bone around the ends of the fragments. Osteoclastic resorption was present even in the longer experiments, but with the bones very



Fig. 9.—Fifteen day experiment: This shows a portion of a small cyst in the defect on the side of the bladder transplant with new bone around the cyst; 32 mm. objective on the left and 16 mm. on the right.

atrophic, the number of osteoclasts was considerably less than in the earlier experiments in which the resorptive process seemed to be more active.

**Bladder Transplants in the Ulna:** In the seven day experiment the defect in the ulna was filled with an organizing blood clot containing masses of bladder epithelium, in some of which the cells had proliferated. In the experiment using the scrapings these cells had formed small cysts. Some of the cysts contained a granular precipitate while others contained small spherules, most of which could be stained with eosin. There was no evidence of bone around the walls of the cysts. The ends of the fragments of bone were apparently dead, as the lacunae were empty, but there was rather marked proliferation of osteogenic

tissue beneath the periosteum and around the ends of the bones, with the formation of some callus and new bone. There was a short finger-like mass of new bone extending out from the medullary canal of the end of one fragment (endosteal bone).

In the fifteen day experiment the blood clot had largely disappeared and the defect was filled with young connective tissue which contained two rather large masses of cartilage. In the center of one of these was



Fig. 10.—Twenty-one day experiment: New bone around the margin of the cyst is lined by bladder epithelium which spans the fragments; 16 mm. objective.

a small cyst lined by bladder epithelium, and around the wall of the cyst was a thick layer of newly formed cancellous bone (fig. 9). Some of this bone merged into the surrounding cartilage and appeared to have been formed by calcification of the cartilage, while in other areas in the same mass the bone apparently had been formed by osteogenic cells in a matrix of connective tissue, showing no evidence of a cartilaginous stage. In most places the epithelium of the wall of the cyst was separated from the surrounding bone by a thin layer of connective tissue or by a homogeneous hyaline layer. Osteogenesis appeared to be

proceeding from the wall of the cyst outward. In another fifteen day experiment in which a strip of membrane was used, a large cyst extended almost across the defect, and some new bone was present along the wall of the cyst next to the callus in the defect.

The ends of the bones in the fifteen day experiment were covered by a cap of new bone, some of the trabeculae of which were continuous with the necrotic ends of the fragments. There was considerably more new bone here than in the experiments lasting seven days.

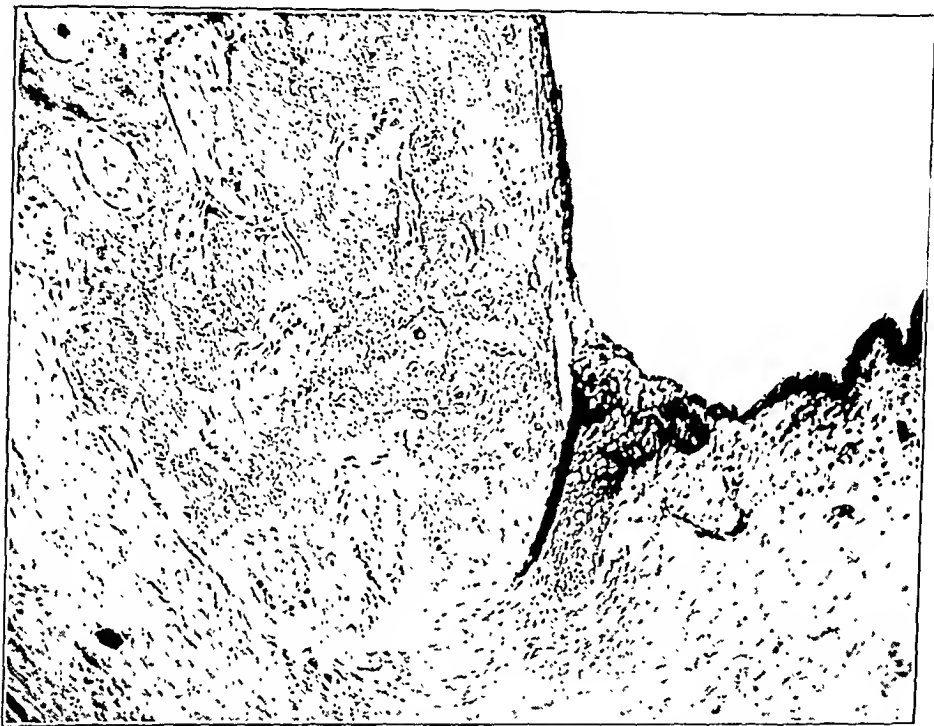


Fig. 11.—Twenty-one day experiment: Note the margin of new bone along one wall of the large cyst lined by bladder epithelium; 16 mm. objective.

In the twenty-one day experiment the defect was spanned by a large cyst, one wall of which was bounded by a thick layer of new bone which was continuous with the subperiosteal new bone around the end of one of the fragments (figs. 10 and 11).

In the longer experiments there was a progressive increase in the amount of callus and bone between the fragments and also a progressive increase in the amount of bladder tissue. The callus tended eventually to span the defect and then to undergo a transformation from an embryonic type to the adult type of bone (fig. 12). In many instances small masses of bladder tissue became incorporated in the callus and formed thin-walled cysts surrounded by bone. In other instances the bladder transplant formed one or more large cysts which often lay along the new

bone which spanned the defect. In the older experiments these cysts were lined by a thin layer of atrophic epithelium, and the walls consisted of a dense collagenic layer which contained very few cells.

It was not possible from a study of the sections of the longer experiments to draw any conclusions in regard to the influence of the bladder transplants on the formation of new bone, as there was no constant relation between the new bone and the bladder transplants. In some sections much new bone was present in areas in which no bladder tissue was seen, while in other sections, or even in other areas of the same section, the new bone was laid down along the cyst wall, or the



Fig. 12.—Fifty-nine day experiment: The cyst is lined by several layers of bladder epithelium with mature bone adjacent to the wall of the cyst; 8 mm. objective.

bladder epithelium was closely applied to a mass of bone, with only a thin basement layer intervening. In some of the older experiments the defect was bridged by a mass of adult bone which contained numerous small cysts lined by bladder epithelium (fig. 13). It was especially noticeable that atrophy of bone did not occur in the presence of the bladder transplants, and that the ends of the fragments tended to remain intact and maintain their normal density or become more dense than normal.

**Abdominal Transplants:** There was marked proliferation of the bladder epithelium and beginning formation of cysts in the seven day specimens. In the fifteen day specimens small cysts had been formed.



and in the twenty-one day specimens the cysts had reached a diameter of 7 mm. The earliest new bone was found in the twenty-eight day specimen. This consisted of several small patches of ossification in the fibrous tissue of the wall of the cyst. Apparently this bone was formed in connective tissue without any preceding formation of cartilage. In all of the older cysts a variable amount of bone was present in the connective tissue adjacent to the walls of the cysts. In some instances this bone formed large plaques, and in others the cysts were surrounded by a shell of bone, or the bone around several cysts had

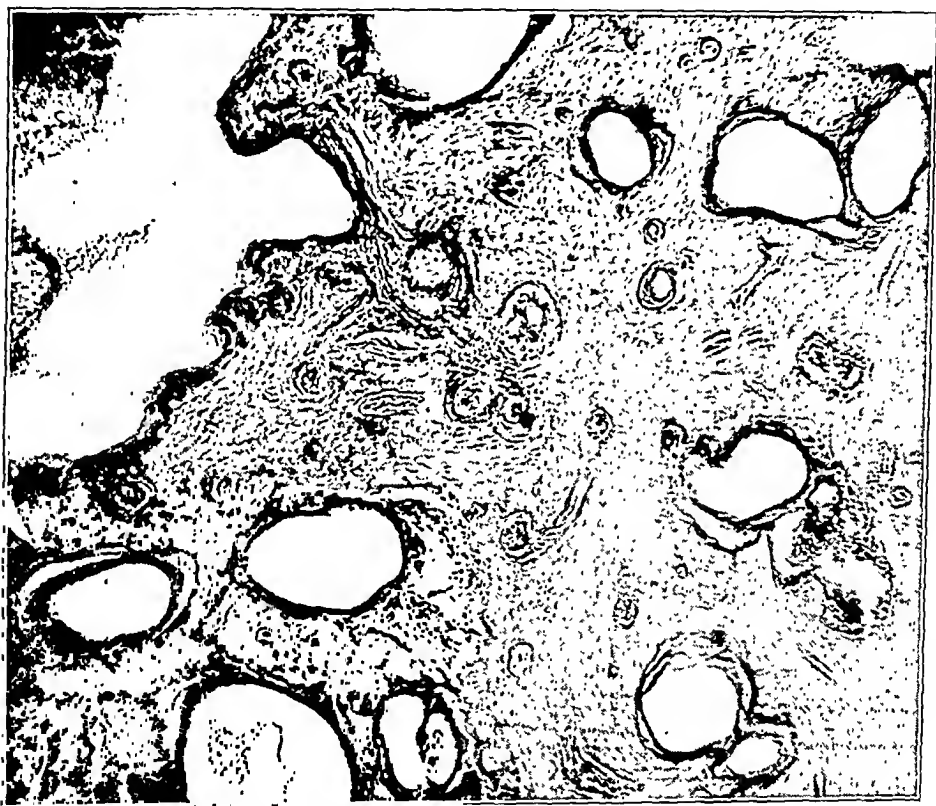


Fig. 13.—Two hundred and seventy day experiment: A portion of a large cyst can be seen in the upper left-hand corner and multiple small cysts scattered through the mature bone which is bridging the defect; 16 mm. objective.

coalesced to form a mass from which the cysts protruded. Hyaline cartilage was occasionally seen in the bone in some of the later cysts, but in no instance was there any indication that cartilage was formed earlier than bone.

#### COMMENT

The results of the experiments reported in this paper indicate that the presence of a growing transplant of epithelium from the bladder tends to stimulate osteogenesis in the defect and causes it to be bridged by new bone in circumstances which would ordinarily result in nonunion.

Microscopic examination of specimens removed from one to four weeks after the operation indicated that the new bone was formed directly under the influence of the growing epithelium of the bladder and was not the result of formation of bone along a strip or sleeve of periosteum bridging the defect. This statement is based on the observation that in the early experiments the new bone usually lay close to the proliferating epithelium and bore no constant relation to the periosteum.

We shall not attempt to settle the question as to whether or not periosteum can be depended on to form bone, as our operations were not executed carefully enough to be of value in this respect. We simply exposed the ulna, split the periosteum, pushed it back with an elevator and removed a section of the shaft—an operation which we would expect to result in nonunion. In young animals a fairly complete sleeve of periosteum was left, but in old animals the periosteum was thin and tore easily, so that no such sleeve was obtained. However, even in old animals there was always a strip of intact periosteum left along the interosseus membrane, so that in all of our experiments the defect was bridged by periosteum. An effort was made to make the control defect in the left ulna as nearly like that in the right ulna as possible.

No effort was made to determine how wide a defect could be bridged by bone under the influence of the bladder transplant. In fact, our effort was to make the defects just wide enough to assure nonunion, and in two instances we failed to do this as is indicated by the fact that union occurred on the control side (figs. 6 and 8). However, the fact that nonunion resulted in fourteen of sixteen controls in which the experiments lasted over thirty-five days is evidence that in the main our defects were adequate, and the observations on formation of new bone and union in the right ulna as recorded in the table are evidence that the bladder transplant in these limbs exerted an influence on the formation of new bone in the defect.

Not only did the bladder transplant cause new bone to form in the defect, but it also tended to prevent the atrophy of the ends of the fragments which uniformly occurred on the control side with nonunion. This was true even in the four instances in which union did not occur on the side with the transplant.

The presence of the transplant in the vicinity of a fracture appeared to result in the production of a larger amount of bone than occurred in similar transplants of bladder epithelium in the abdominal wall. Not only this, but the bone appeared earlier (after fifteen days in the defects and after twenty-eight days in the cysts in the abdominal wall). This was partly due to the fact that some osteogenesis was caused by the fracture, but experiments in progress indicate that the presence of a

reservoir of calcium in the vicinity of a bladder transplant in the abdominal wall results in the production of more bone in the wall of the cyst than occurs in a similar transplant which is not close to a calcium depot.

We are not yet able to explain the mechanism by which the bladder transplant causes formation of bone. As we have already stated, the bone was usually formed directly in the connective tissue and was not preceded by the formation of cartilage. It is possible that the bone is due to the presence of a local excess of calcium, and that this calcium is secreted by the epithelial cells of the transplant. This theory is in accord with the observations of Huggins,<sup>1</sup> who noted that the fluid in the cysts contained a higher concentration of calcium than did the blood of the same animal.

We have considered the possibility that the bladder epithelium might contain some substance which tends to cause formation of bone. Working on this hypothesis we have made various kinds of extracts of bladder epithelium and injected them into the tissues around experimental fractures, but thus far the results of these experiments have been negative.<sup>5</sup>

#### CONCLUSIONS

Homologous transplants of epithelium from the urinary bladder tend to cause formation of bone in their vicinity, and if they are placed in a defect of bone they tend to cause union in defects which would ordinarily result in nonunion.

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5. Copher, G. H.; Key, J. A., and West, E. S.: Influence of Bladder Extracts and Viosterol on Healing of Fractures and Bone Defects, *Proc. Soc. Exper. Biol. & Med.* **29**:646 (Feb.) 1932.

# ACANTHOMA OF THE ANUS

## REPORT OF THREE CASES

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AND

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LOS ANGELES

The occurrence of an acanthoma at the anus is sufficiently rare that few observers are privileged to study more than 1 case. In a study of 1,097 cases of malignant tumor occurring in 9,000 consecutive autopsies performed in the Los Angeles County General Hospital, we have had the opportunity to study 3 cases of epidermoid carcinoma which arose in the anorectal region. This constituted an incidence of 1 per cent of all the primary new growths found in the gastro-intestinal tract, and approximately 3 per cent of the carcinomas arising in the large bowel. Lynch<sup>1</sup> in a review of 491 cases of cancer of the rectum and pelvic colon reported 15 cases of epithelioma, an incidence of 3 per cent. Pack,<sup>2</sup> after an extensive study of anal and rectal neoplasia, concluded that epithelioma in this region was comparatively rare, with an incidence of from 3 to 4 per cent. Brofeldt<sup>3</sup> studied 260 cases of rectal tumors and reported 5 cases of squamous cell carcinoma, 2 of which were not verified by microscopic study. The cases reported in our study occurred in a series of 46 malignant tumors originating in the anorectal region,<sup>4</sup> thus giving an incidence somewhat higher than that reported by other observers.

The literature of the past two decades contains reports of 40 cases of anal acanthoma. Kerr,<sup>5</sup> in 1913, reported the successful resection of a cauliflower-like mass arising at the anal mucocutaneous junction which proved histologically to be an epidermoid carcinoma. Lynch,<sup>1</sup> in 1917, reported 15 cases of anal epithelioma without attempting to

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From the Department of Pathology (Dr. Newton Evans, Director), Los Angeles County General Hospital.

1. Lynch, Jerome M.: Cancer of the Rectum and Pelvic Colon, *J. A. M. A.* 69:1775 (Nov. 24) 1917.

2. Pack, George T.: The Pathological Aspects of Anal and Rectal Neoplasia, *Internat. Clin.* 2:77 (June) 1927.

3. Brofeldt, S. A.: Zur Pathogenese des Plattenepithelkrebses der Pars analis recti. *Acta Soc. med. ienn. duodecim* 8:3, 1927.

4. Harding, Warren G., 2d. and Hankins, Franklyn D.: Post Mortem Observations of 118 Carcinomas of the Large Bowel, *Am. J. Cancer* 17:634 (Feb.) 1933.

5. Kerr, H. H.: Epithelioma of the Anus. *Surg., Gynec. & Obst.* 16:108 (Jan.) 1913.

describe the clinical course or the pathologic findings in the disease. In a case of squamous cell carcinoma of the anus roentgen therapy was used by Lockhart-Mummery<sup>6</sup> in 1923. One such tumor, arising at the site of an imperforate anus, was described by Mecray<sup>7</sup> in 1926. Wallon,<sup>8</sup> Hawe<sup>9</sup> and Plisson<sup>10</sup> reported cases in 1927. In addition Brofeldt<sup>3</sup> reviewed the pathogenesis of pavement cell carcinoma of the anal canal and reported 3 cases which were verified histologically. In 1930 Angevine<sup>11</sup> studied at autopsy a case showing 3 distinct malignant rectal tumors, 1 of which was an acanthoma. Rosser,<sup>12</sup> in studying the relationship of chronic inflammatory lesions of the rectum to neoplasia, described 3 microscopically proved epidermoid carcinomas of the anus. Gabriel,<sup>13</sup> in a study of the end-results in the treatment of 370 cancers of the rectum, recorded 12 cases of squamous cell carcinoma of the anus and anal canal. Of these, 8 were assessed as "operable" and 4 as "inoperable." Recently Lockhart-Mummery<sup>14</sup> reported the treatment of an epithelioma of the anus occurring in a man 56 years of age. A combination of radon seeds and radium needles inserted beneath and around the tumor was used. There was no evidence of recurrence at the time of reporting, nearly one year after treatment.

#### REPORT OF CASES

**CASE 1.—History.**—Mr. Y. V., a Mexican laborer, aged 35, presented himself in the outpatient department in June, 1926, complaining of severe constipation and a stinging pain in the anorectal region during defecation followed by a slight amount of bleeding. A diagnosis of condyloma of the anus and cryptitis was made and appropriate therapy was advised. He refused treatment, and was not seen again for two years. On his return, in 1928, he complained of "piles" which had caused considerable pain, difficulty in expelling the feces and occasionally bright

6. Lockhart-Mummery, J. P.: *Diseases of the Rectum and Colon*, New York, William Wood & Company, 1923.

7. Mecray, P. M.: *Epithelioma of the Anus in a Case of Imperforate Anus*, S. Clin. North America **6**:1623 (Dec.) 1926.

8. Wallon, E. M.: *Epithélioma anal guéri par le radium après dérivation temporaire des matières*, Bull. Soc. franç. de dermat. et syph. **34**:436 (July) 1927.

9. Hawe, P.: *Carcinoma, a Complication of Piles*, Brit. M. J. **2**:349 (Aug. 27) 1927.

10. Plisson, M. L.: *Epithélioma ano-rectal*, Progrès méd. **42**:1408 (Sept. 10) 1927.

11. Angevine, D. M.: *Three Primary Malignant Epithelial Tumors of the Ano-Rectal Region Occurring in One Person*, Canad. M. A. J. **23**:38 (July) 1930.

12. Rosser, Curtice: *Etiology of Cancer of the Anus*, Am. J. Surg. **11**:328 (Feb.) 1931.

13. Gabriel, W. B.: *End Results of Perineal Excision and Radium in the Treatment of Cancer of the Rectum*, Brit. J. Surg. **20**:234 (Oct.) 1932.

14. Lockhart-Mummery, J. P.: *Epithelioma of Anus Treated by Radium*, Proc. Roy. Soc. Med. **26**:589 (March) 1933.

red blood in the stool. During the previous three weeks he had suffered severe pain in the right side of the chest, associated with coughing.

*Physical Examination.*—Examination revealed an emaciated man of 37, apparently in distress. The right side of the chest showed the classic findings of a massive pleural effusion. There was exquisite tenderness to deep palpation in the right side of the hypochondrium, without other abdominal findings. A girdle ulcer with a firm base occupied the lower half of the anal canal, at the base of which was a "sentinel" pile. An ulcerative proctitis extended above this ulcer for  $2\frac{1}{2}$  inches (6.4 cm.). A blood test showed 17,600 white cells, with 79 per cent polymorphonuclears. The sputum was negative for the tubercle bacillus. The Wassermann reaction of the blood was 4 plus.

*Course.*—The course was progressively downward, with a septic temperature and an increase in the severity of the symptoms in the chest. Death occurred after two months.

*Autopsy.*—The essential pathologic findings exclusive of the acanthoma were limited to an extensive amebic colitis and an abscess of the liver with diaphragmatic extension resulting in empyema on the right side. The anus was deeply fissured, with a large necrotic ulcer. No local extension or regional adenopathy was found. The microscopic sections of the anal ulcer showed a squamous cell carcinoma graded 1 as described by Broder.

*CASE 2.—History.*—Mrs. P. R., aged 40, was admitted to the Los Angeles County General Hospital with a complaint of malaise, weakness, loss of appetite, severe constipation and difficulty in expelling the feces. She first noticed these symptoms three months before admission. One month after the onset she was troubled with flatulence which had been progressively worse until the date of admission. The constipation virtually amounted to obstipation during the immediately preceding month. Twice during the course of the disease she had noticed bleeding from the rectum which she ascribed to hemorrhoids.

*Physical Examination.*—Examination revealed a well nourished Mexican woman not in acute distress. The physical findings were essentially normal except for the local pathologic process. The posterior wall of the vagina was pushed forward by a hard mass, giving the impression that the rectum was packed with feces. Digital examination of the rectum revealed a coarsely nodular, irritable, ulcerated mass originating at the anorectal junction and extending upward into the pelvis beyond the length of the examining finger. The lesion occupied the entire circumference of the rectum except for a strip along the anterior wall which measured 1 cm. in width. Proctoscopic examination showed the lesion to extend for approximately 5 cm. above the anorectal junction. The perirectal tissue was moderately indurated. Laboratory examination, including the injection of a radiopaque enema, gave negative results except for a Wassermann reaction of 1 plus and a Kahn reaction of 2 plus.

*Course.*—A single loop colostomy was made, and the distal loop transplanted to the pelvic retroperitoneal space. The postoperative course was hectic, and on the nineteenth day a perineal incision was made into a large perirectal abscess. Ten days later the lower loop of the colostomy was resected, the abdominal approach being used. The postoperative course was stormy. Death occurred in four days with clinical evidence of acute generalized peritonitis.

*Autopsy.*—The significant organic changes were limited to the neoplasm and the changes incidental to the surgical assault directed toward its destruction. The rectum and the anal canal remained in the pelvis. The mucosa of the portion of

bowel immediately proximal to the tumor was superficially ulcerated, but showed no other essential disease. At the anorectal junction was a firm mass, the lower margin of which was polypoid, ragged, necrotic, foul smelling and ulcerated. The neoplastic tissue above the ulcer produced a considerable degree of stenosis. The perirectal tissue was indurated and in the region of the posterior vaginal wall showed the remains of an abscess which was draining into the vagina. A careful search of the pelvic lymphatics and the inguinal nodes showed no metastatic deposits, either in the gross specimen or by microscopic section. The abdominal cavity showed the typical changes of acute generalized peritonitis.

Histologic examination of the growth revealed a typical malignant growth of epithelial cells of the squamous variety. Numerous pearl bodies were present. The carcinomatous cells were found invading the muscularis of the bowel, but



Fig. 1 (case 3).—Exophytic type of acanthoma of the anus.

none was found in the perirectal fat. An extensive infiltration of polymorphonuclear wandering cells was present throughout the tumor. Microscopically the tumor was graded according to Broder's classification as grade 1.

*CASE 3.—History.*—Mr. J. H., aged 60, was admitted to the Los Angeles County General Hospital, complaining of constipation for many years, a progressively enlarging ulcerating growth at the anus and pain in the region of the tumor when sitting. The growth appeared nine months previously as a "bluish pimple" in the perianal skin. The tumor was firm and painless, and during the early portion of its growth invaded the anal mucosa. During the immediately preceding three months the growth became painful to pressure and bled when traumatized. The patient's history was irrelevant except for a syphilitic infection thirty years before admission which had been vigorously treated.

*Physical Examination.*—Examination revealed a well preserved and well nourished white man who did not appear to be acutely ill. The essential physical find-

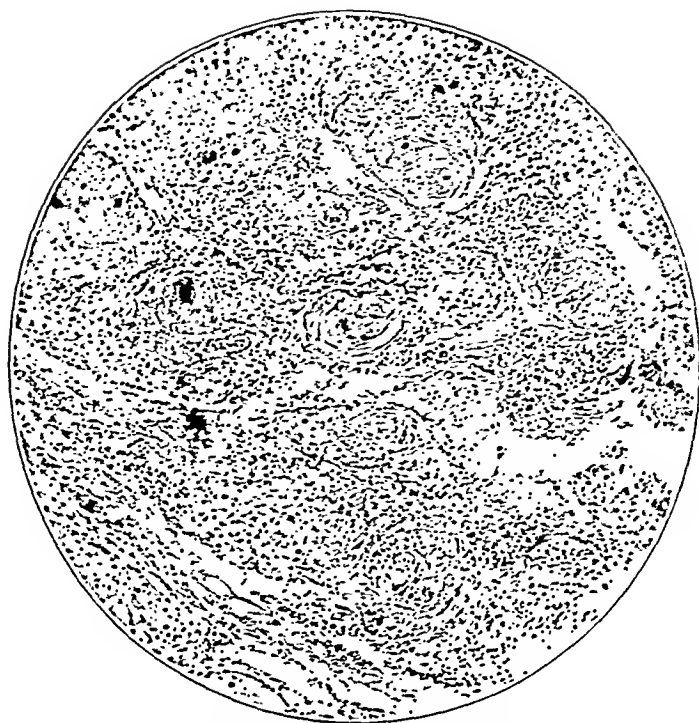


Fig. 2 (case 3).—Photomicrograph of well differentiated tissue with numerous pearl bodies; hematoxylin and eosin stain:  $\times 165$ .



Fig. 3 (case 3) —Photomicrograph of squamous cell epithelium. An occasional mitotic figure is seen. hematoxylin and eosin stain:  $\times 309$ .



ings were limited to the anal growth. The anal orifice was obscured by an elliptic, velvety, papillomatous, ulcerated and necrotic tumor 12 by 8 cm. in diameter which occupied the perineum from the central tendinous point posteriorly to a point 1 cm. anterior to the tip of the coccyx. The lateral margins were approximately 1 cm. medial to the tuber ischii. The central portion was deeply fissured and ulcerated, and discharged a seropurulent fluid. The margins were dusky, smooth, rolled and sharply limited. The tumor was hard except in the midportion, where necrosis had taken place. The tumor caused considerable constriction of the anal orifice, and extended upward to the lower surface of the levator ani. No enlarged lymph nodes were found in the pelvis or in the inguinal region. The laboratory findings were negative except for a Wassermann and Kahn reaction of the blood serum of 4 plus.

*Course.*—The entire growth and the fat in the ischiorectal fossa were resected with the Percy cautery following removal of a specimen for biopsy. The patient failed to respond postoperatively, and the condition became toxic. He died of circulatory failure on the sixth day following the operation.

*Autopsy.*—A complete examination of the body revealed no remaining carcinoma. Otherwise the essential changes were a marked generalized arteriosclerosis with coronary sclerosis. Histologic examination of the specimen removed at operation showed a grade 1 (Broder) squamous cell carcinoma.

#### COMMENT

Acanthomas of the anus usually arise at the mucocutaneous junction. The lesion is sharply demarcated and becomes ulcerated late in its course. The growths may be of the exophytic, exuberant type (case 3) or the endophytic type which occupies the anal canal without producing an externally visible tumor, as illustrated by cases 1 and 2. Clinically the tumor produces a period of constipation of varying length before localizing symptoms appear. Later, the patients complain of a sense of fulness in the rectum, difficulty in expelling the feces and a minor amount of bleeding, and in the exophytic type the tumor is often described. The endophytic type is frequently associated with hemorrhoids. Early ulceration associated with excruciating pain, as emphasized by Rankin, Bargen and Buie,<sup>15</sup> was not prominent in our cases.

Several views have been expressed regarding the etiology of this neoplasm. The exciting cause is veiled in the obscurity enclosing the etiology of malignant growths elsewhere in the body. Pack<sup>2</sup> supports the Cohnheim theory of "cell rest" and relates its probability to the complex embryologic development of this particular region. The theory ascribing the development of cancer to the changes resulting from chronic irritation has been especially emphasized in this location owing to the nature of the secretions present, the inability to maintain strict cleanliness, and, associated with these factors, the occurrence of such

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15. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: *The Colon, Rectum and Anus*, Philadelphia, W. B. Saunders Company, 1932.

lesions as fissures, fistulas and hemorrhoids. Opposed in part to that theory is the case described by Mecray<sup>7</sup> of an epidermoid carcinoma occurring at the site of an imperforate nonfunctioning anus. It must be conceded, however, that in this case the element of chronic irritation is not completely excluded. The ulcerative colitis due to *Endameba histolytica* in case 2 is an added factor of chronic irritation. Brofeldt<sup>2</sup> maintained that leukoplakia is frequently present in the anal canal and has a relation to anal cancer similar to that which its homolog in the oral cavity has to the development of buccal carcinoma. In the 3 cases reported here it seems noteworthy that a positive Wassermann reaction of the blood serum occurred in each case, although the reaction present in case 2 was only 1 plus with an accompanying Kahn reaction of 2 plus. The reactions were repeated in each case. These cases were not seen sufficiently early to determine whether this factor operated through the development of leukoplakia. The one patient seen two years before the tumor was diagnosed was thought to have an anal condyloma. In the case reported by Wallon<sup>8</sup> a diagnosis of "mucous patches" was made three years before the acanthoma developed, and the patient was given appropriate antisyphilitic treatment. It appears that the syphilitic infection furnished a favorable soil on which the epithelioma developed. In cases 1 and 2 of this report an associated rectal lesion produced chronic irritation complicating the problem of determining the underlying cause.

From the point of view of pathology these growths are of a comparatively low degree of malignancy. Each of the three cases we studied was classified as grade 1 (Broder). The tumor is at times found penetrating the muscular coats of the bowel, suggesting the possibility of direct extension into the ischiorectal fossae. None of the cases described showed metastases to the regional nodes. Waring<sup>16</sup> discussed the mode of metastases to the inguinal nodes via a lateral and a medial channel. No secondary deposits were found in this group of nodes although a careful search for them was made.

The therapeutic deductions from these data are obvious. The lesion could be cured in its early stages by local removal, preferably by the cautery, as suggested by Charles Mayo.<sup>17</sup> Later in the course of the disease the anus, anal canal and lower portion of the rectum should be radically resected and an extensive dissection of the inguinal nodes accomplished. For epitheliomas graded 3 and 4 (Broder) Rankin,

16. Waring, H. J.: *Surgical Treatment of Malignant Disease*, New York, Oxford University Press, 1928, p. 127.

17. Mayo, Charles: *The Choice of Operative Procedure in Cancer of the Rectum and Pelvic Colon*, Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1916, vol. 8, p. 322.

Bargen and Buie<sup>15</sup> advocated treatment by irradiation in preference to surgical intervention. Wallon,<sup>8</sup> Lockhart-Mummery<sup>18</sup> and Gabriel<sup>13</sup> have reported success in curing this lesion by irradiation, although the degree of differentiation of the tumor as shown by its histopathology does not particularly suggest that it is radiosensitive.

#### SUMMARY

1. Forty acanthomas of the anus reported in the literature of the past two decades are reviewed.

2. The clinical course and findings at autopsy in 3 cases of acanthoma of the anus in a series of 46 malignant tumors of the anorectal region are recorded.

3. Each of the 3 patients presented an associated syphilitic infection, evidenced by positive Wassermann and Kahn reactions of the blood serum.

4. These tumors are of a comparatively low grade of malignancy. Each of the 3 tumors reported here was classified grade 1 (Broder).

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18. Lockhart-Mummery (footnotes 6 and 14).

# A NEW INSTRUMENT FOR INTRAVESICAL IRRADIATION

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AND

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Therapy with ultraviolet rays from a quartz mercury vapor arc lamp has for a long time been an important part of treatment of postoperative and inoperable genito-urinary tuberculosis. The older type of air-cooled quartz mercury vapor arc lamp, also the newer more powerful variety, and the water-cooled quartz mercury vapor arc lamp have been utilized. The air-cooled lamp is almost a specific in the healing of sinuses following nephrectomy and epididymectomy for tuberculosis. Similar exposures over the regions of the bladder and kidneys at regular intervals over long periods are given as a routine in the treatment of urinary tuberculosis. Since therapy of this kind has been useful externally it is reasonable to think that it might have a good effect in the bladder if it could be suitably applied. However, we have not been able to employ it satisfactorily until recently.

Caulk and Ewerhardt<sup>1</sup> reported treatment by direct internal ultraviolet irradiation of the bladder of a patient from whom a tuberculous kidney had been removed several years previously and who still had persistent ulceration in the bladder. Using a cold quartz orificial applicator, insulated to protect the urethra, they arranged a device to introduce both air and ultraviolet irradiation into the interior of the bladder. They stated that as far as they could determine it was the first time that such a technic had been attempted.

A few months later we obtained a quartz mercury vapor arc lamp of the vacuum discharge type, with a bladder applicator, constructed according to our specifications.<sup>2</sup> The applicator is made of a new material produced for physical, photochemical, physiologic and thera-

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Read before the Section on Genito-Urinary Diseases of the New York Academy of Medicine.

1. Caulk, John R., and Ewerhardt, F. H.: Direct Internal Irradiation of Ultraviolet to the Bladder, *Arch. Phys. Therapy* **13**:325 (June) 1932.

2. Mr. Frederic W. Robinson of the Hanovia Chemical Company cooperated in the manufacture of this instrument.

peutic experimental work and also for study of the "Raman effect." The tube is made of clear fused quartz to transmit the rays readily and operates at a little above room temperature. It is said to be practically monochromatic, and approximately 85 per cent of the generated light

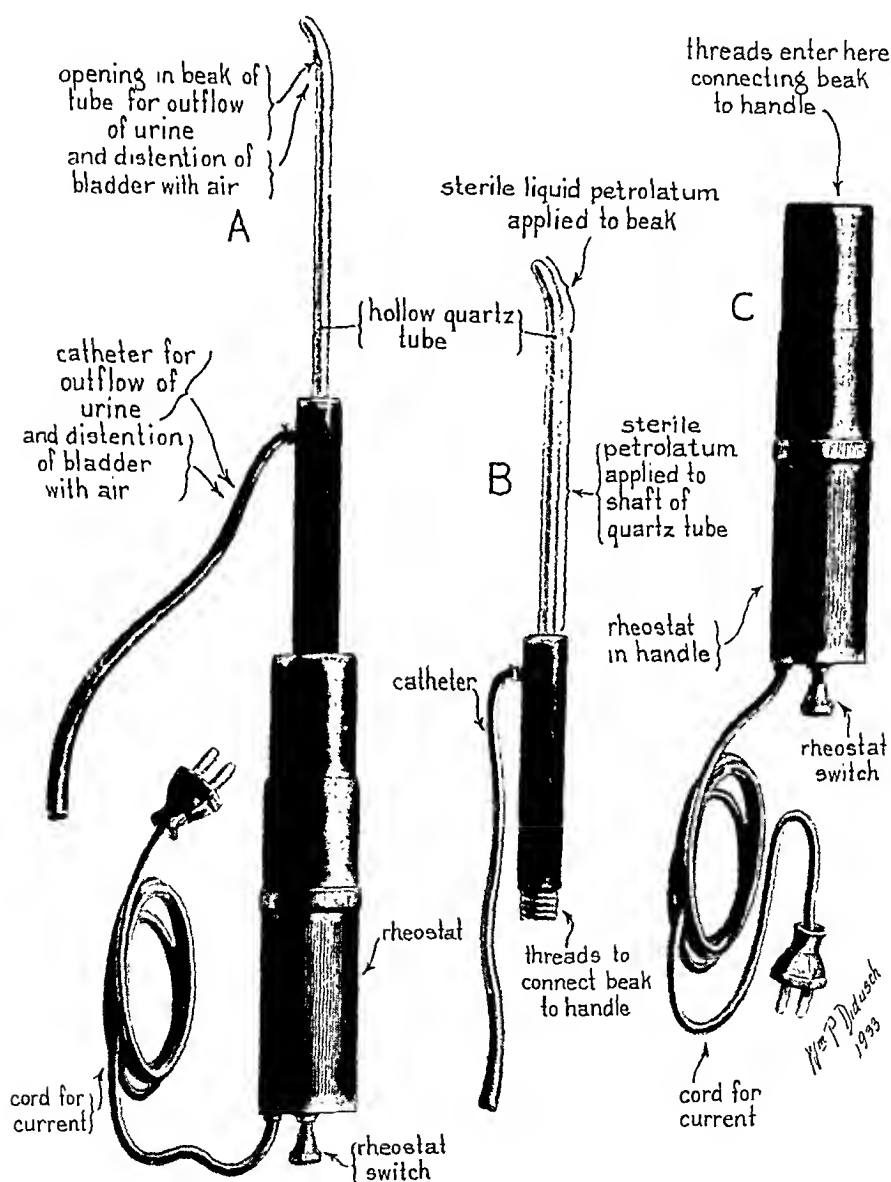


Fig. 1.—*A* shows the assembled instrument, consisting of rheostat, cord, catheter for the overflow of urine and distention of the bladder with air and the hollow quartz tube for the passage of the irradiation current. *B* and *C* show the instrument disassembled.

is in the band of 2,537 angstroms. The applicator is about the same length and shape as a Brown-Buerger cystoscope, measuring about 24 French in diameter. There is an extra tube built into the quartz

with a circular opening or eye at the distal end and with a rubber tube attached to the other extremity. The tube is for the purpose of catheterizing the bladder. After the bladder is emptied air is insufflated through the tube to distend the organ slightly before irradiation. Following the treatment an instillation can be made through the tube if desired. The applicator, except at the distal end, is smeared with sterile petrolatum to prevent the irradiation of the urethra, and sterile liquid petrolatum, which permits the passage of the rays, is used on the part that enters the bladder. The instrument offers a simple and practical

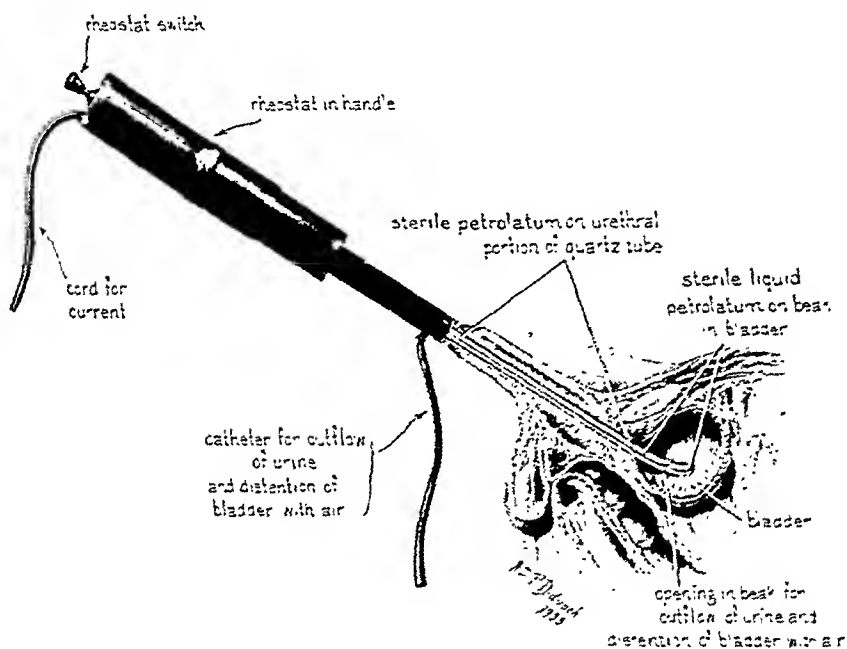


Fig. 2.—A sagittal section of the bladder and urethra with the instrument in place and the bladder distended with air for the dissemination of irradiation in the diseased bladder.

means of irradiation of the interior of the bladder. The bladder can be emptied, then distended with air without pressure and irradiated at one operation and with little discomfort to the patient. The applicator passes through the urethra easily and can be used equally well in either male or female patient. Exposures up to thirty seconds have thus far been used, depending on the reactions elicited. The reactions are of a transitory character, lasting for a few hours.

Eleven patients are receiving internal treatments. In four the condition seems to be definitely improved, in four others slightly improved, and in three there is no improvement. Several have badly damaged

bladders owing to extensive involvement, which offers a severe test for any form of therapy. To show the kind of patients treated the series is briefly described.

CASE 1.—A woman, aged 22, married, weighing 74.1 Kg., had tuberculosis of the right ankle in childhood which healed after a year. About two and a half years ago, following childbirth, she began to have urinary frequency, hematuria, pain in the bladder and burning on urination. A right nephrectomy for tuberculosis was done on Aug. 12, 1931. The wound healed in two weeks. The urinary frequency has persisted day and night with pain in the bladder. The urine still contains acid-fast bacilli in catheterized specimens. The capacity of the bladder is 30 cc., the walls are trabeculated, there are ulcerations at the neck and on the right side, and the right ureteral opening is atrophied (the left is apparently normal). The patient has been treated for five months with intravesical irradiation, and there has been marked improvement. The urinary frequency has lessened, and the pain in the bladder has diminished.

CASE 2.—A woman, aged 25, married, weighing 47.8 Kg., had tuberculosis of the lungs in 1924, which was arrested after a year in a sanatorium. Three years ago urinary burning and frequency developed. A diagnosis of bilateral inoperable renal tuberculosis was made. A year later the left kidney suppurated, the general condition became grave, and a nephrectomy was performed as an emergency measure to prolong her life. The wound healed after nine months. The urinary frequency was lessened, but continued, with pain in the bladder. Urine taken from the bladder reveals acid-fast bacilli. She has received irradiations to the bladder for about five months, although she has been somewhat irregular in her attendance at the clinic. There has been a slight improvement in the symptoms.

CASE 3.—A man, aged 30, married, weighing 70.8 Kg., had pain in the right lumbar region in April, 1929, which became more severe and was accompanied by a high fever. A right nephrectomy for tuberculosis was done at another hospital in April, 1929. He felt well until May, 1932, when a sinus developed in the scar of the nephrectomy which still drains rather profusely. A few months later he noted urinary frequency and was referred to our clinic for treatment. The interior of the bladder shows a little roughening of the mucosa at the fundus and slight injection of the trigon. There are acid-fast bacilli in the urine. He has a pulmonary lesion which is apparently inactive. Because of the unusual history of the sinus and its atypical character, roentgenograms were made of the spine in the lumbar region which revealed spinal caries. It is believed that the sinus is due to the caries, and the patient is now receiving orthopedic care. The bladder has been irradiated for three months and the urinary symptoms are slightly lessened.

CASE 4.—A woman, aged 28, married, weighing 51.9 Kg., became pregnant in 1922; at the fourth month general edema developed. Her physician diagnosed the condition as a "pus kidney," and a therapeutic abortion was done. Shortly afterward urinary frequency occurred, which gradually increased in severity. A right nephrectomy for tuberculosis was done in May, 1930. Since then the patient has had slight urinary frequency and pain on urination. The disease seems to be of a relapsing type, as there are periods of almost complete relief which are broken by a recurrence of marked symptoms. The urine contains a large amount of pus and acid-fast bacilli. There is a mild thyroid disturbance at times. She

has received irradiation for three months, and the condition is improved; however, the remittent nature of the disease presents difficulties in determining the condition.

CASE 5.—A woman, aged 22, unmarried, weighing 48.7 Kg., had tuberculous peritonitis in 1924, and after several years of hygienic care had no further symptoms. Since 1930 she has had pain in the region of the kidneys, mostly on the right side, with urinary frequency and burning. The condition was diagnosed as inoperable bilateral renal tuberculosis. The capacity of the bladder is 130 cc., and the interior is essentially normal except for reddening around the left ureteral opening, below which there is a red bleb. The bladder has been irradiated for four months, and while there has been occasional temporary lessening of pain after the treatments, the condition has not improved.

CASE 6.—A woman, aged 24, unmarried, weighing 50.2 Kg., had tuberculosis of the lungs in 1928, which apparently became arrested after seven months in a sanatorium. There has been an extensive pustular acne for the last two years. Pus in the urine was discovered four years ago. Urinary frequency, both day and night, and pain in the back developed a few months after finding pus in the urine. The patient lost weight and strength. A right nephrectomy for tuberculosis was performed at another hospital on June 6, 1932. She was subsequently referred to our clinic suffering with urinary frequency, pain in the bladder and occasional hematuria. She has received internal irradiation for two months, and the condition has improved.

CASE 7.—A woman, aged 25, unmarried, weighing 42.5 Kg., began to have urinary frequency in 1928. It became more severe, and the right kidney was removed for tuberculosis on Nov. 14, 1930. The frequency continued and an ulceration in the bladder underwent fulguration several times without lasting results. Tuberculosis of the lungs developed in 1931, which became quiescent after a year of rest, diet and fresh air. The urinary symptoms persisted. The bladder is extensively diseased; the capacity is 30 cc., and there are numerous trabeculations and disseminated ulcerations, particularly in the regions of the ureteral openings. Internal irradiation has been given for four months, with definite symptomatic improvement.

CASE 8.—A woman, aged 40, married, weighing 66.8 Kg., has had pain in the bladder before urination, great urinary frequency and pain in the kidneys and along the urethra since 1924. She has been treated by numerous physicians and at several hospitals without relief. Endoscopy showed ulcerations of an odd villous appearance along the urethra. Cystoscopy showed the same productive form of ulcerations within the bladder, widely distributed and somewhat ecchymotic. The capacity of the bladder is about 30 cc. The lesions are not definitely characteristic of tuberculosis. Many remedies and various therapeutic procedures have been tried without affording relief. Internal irradiation for five months has not given periods of lasting relief. Recently longer irradiation, up to thirty-five seconds, of both urethra and bladder, followed by an instillation of 1 ounce (28.34 Gm.) of 2 per cent of a preparation similar to oil of cajuput in olive oil, have afforded symptomatic relief for from twenty-four to thirty-six hours after treatment.

CASE 9.—A woman, aged 31, married, weighing 59.8 Kg., at the age of 13 had pleurisy with effusion: aspiration was performed and a large amount of fluid removed. Recovery occurred after a long period. During June, 1931, pain occurred in the bladder and right kidney, accompanied by slight urinary frequency and burning. She was treated for five months in a sanatorium for tuberculosis, where



it was determined that there was no pulmonary involvement. A right nephrectomy for tuberculosis was performed on June 15, 1932, at another hospital, and the wound healed in fifteen days. The urinary frequency and pain in the bladder continued, and she was referred to our clinic. The capacity of the bladder is 110 cc.; the left ureteral opening is enlarged, the right ureteral opening is not visible and there is an irregularly shaped ulcer of dull appearance above the region of the right ureteral opening. The patient has received internal irradiation for about five months and there is a little improvement.

CASE 10.—A woman, aged 32, unmarried, weighing 61.1 Kg., had hematuria in February, 1924, followed by urinary frequency and pain in the bladder. A right nephrectomy for tuberculosis was performed on Nov. 21, 1924, at another hospital. After two years of treatment with rest the symptoms disappeared. Urinary frequency recurred in 1930, and later she was referred to our clinic. The capacity of the bladder is 75 cc., the right ureteral opening is not visible, the left is distended and distorted and there is extensive trabeculation with widespread ulcerated hemorrhagic areas. The urine is turbid, and there is macroscopic evidence of blood and considerable pus. Internal irradiation for five months has made little if any change, except a temporary lessening of the symptoms.

CASE 11.—A woman, aged 47, married, weighing 81.6 Kg., at the age of 9 had a disease of the bone in the left forearm, apparently tuberculous, which healed after a year. In 1925 urinary frequency developed, with pain in the bladder and general debility. A right nephrectomy for tuberculosis was performed a year later, and the wound healed in a short time. The urinary frequency continued for two or three years, then subsided; fulguration was used twice for the ulcerations in the bladder. Since then the only symptoms have been occasional pain in the bladder and a slight intermittent urinary frequency. The capacity of the bladder is 230 cc., and the wall is essentially normal except for a little redness around the left ureteral opening. She has received internal irradiation for six weeks, and there has been some improvement.

#### COMMENT

It is apparent that no attempt was made to select the patients to receive the irradiation, as many have lesions in the bladder which are very extensive and function is probably partially crippled. No conclusions can be drawn from so small a series, but it would seem that post-operative treatment of this kind is indicated after a nephrectomy in patients with small lesions in the bladder that are not of long standing. Fresh air and therapy with a quartz mercury vapor arc lamp hasten the healing of external lesions, and there is reason to believe that similar results should follow the same treatment of internal lesions. Even in widespread involvement of the bladder several patients have thought that there was lessening of sensitivity in the bladder. This form of therapy seems better tolerated than any other local treatment that we have tried. The applicator was planned with the thought that there must be as little local disturbance as possible, and it seems successful in that respect. Patients who have received external therapy with a quartz mercury vapor arc lamp are usually willing to try the treatment internally.

It has been suggested that irradiation might have some field of usefulness in urology other than in the treatment of urologic tuberculosis. Eighty-five per cent of the generated light is said to be in the band of 2,537 angstroms, which is considered bactericidal. A patient with chronic posterior gonorrheal urethritis is now being treated and it is hoped to treat a sufficient number with a similar infection on which to base worth-while conclusions.

Caulk and Ewerhardt noted the disappearance of an infection by colon bacilli in their patient after four periods of irradiations. Other observers have reported that the use of a quartz mercury vapor arc lamp is effective against colon bacilli. We have not yet begun treatment of patients with such an infection.

#### CONCLUSIONS

1. The instrument we have used seems to be satisfactory for emptying the bladder, introducing air and irradiating the wall of the bladder. In the series of patients treated the results have been encouraging and warrant further trial of the procedure.

2. This instrument may also be utilized to treat sinus tracts caused by tuberculosis in any part of the body.

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# TRAUMATIC VASOSPASM

## A STUDY OF FOUR CASES OF VASOSPASM IN THE UPPER EXTREMITY

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Disturbances of the sympathetic impulse in the extremities are still too little understood. From time to time reports of conditions suggesting dysfunction of the sympathetic system affecting the blood supply reach the literature. The clinical expressions of sympathetic dysfunction in any group of cases are apt to be variable and difficult to correlate. Among the array of conditions in which hyperactivity of the sympathetic system can be described, traumatic vasospasm may be picked out as a more or less definite entity. Individual instances of traumatic vasospasm are so different from each other in their details that the total clinical picture is not easy to visualize. They have two factors in common: (1) trauma, usually received at some time considerably earlier than the patient is seen, and (2) evidence of vasospasm. Confusion arises because one often sees additional disturbances of somatic sensory and motor function as well as so-called trophic changes. These disturbances are sometimes bizarre in that they bear no anatomic relationship to the injury or to the area affected by arterial spasm. Some patients present an extraordinary variety and intensity of disturbances; in others none may be present. Their relationship to or identity with hysteria is usually debatable. The reaction to treatment in individual cases is correspondingly irregular. Until a much larger number of these curious conditions are recorded in detail knowledge of them will remain defective. For that reason I am reporting four cases of sympathetic disturbance following injury, all of which can probably be classed as traumatic vasospasm. Attention may be called to a contribution by Morton and Scott<sup>1</sup> in which these and related conditions are discussed in full.

### REPORT OF CASES

CASE 1.—*Superficial Wound of Palm.—Infection.—Vasospasm of five months duration. Unanatomic sensory disturbance. Loss of forearm motor power with spastic state of muscles. Rapid complete recovery following fever.*

W. A. M., a white man, aged 28, a laborer, entered the hospital on Aug. 20, 1930, two weeks after a superficial laceration in the palm of the right hand. At

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Abridged from a paper read before the Ohio County Medical Society, Wheeling, W. Va., April 14, 1933.

1. Morton, J. J., and Scott, W. J. M.: Some Angiospastic Syndromes in the Extremities, *Ann. Surg.* **94**:839 (Nov.) 1931.

first he continued to work. Three days later the hand became swollen and painful, but he still worked for three more days, and then went to bed and applied poultices for about a week. The wound in the palm was then opened by his local physician. The operation was followed by an evidence of spreading infection, including lymphangitis, and he was referred to the hospital. Under nitrous oxide anesthesia the midpalmar space was drained with prompt and apparently complete recovery. He was discharged four days later.

The wound drained for a period and then healed. When attempting to use the hand, the patient found much weakness in the fourth and fifth fingers with diminution in sensation in this area. The scar was painful. He noticed "poor circulation" in the right arm which felt "heavy and dull." He also noticed that it was cooler than the other hand. There was no pain except on movement. Exposure to cold caused numbness of the inner half of the hand. He was readmitted to the hospital

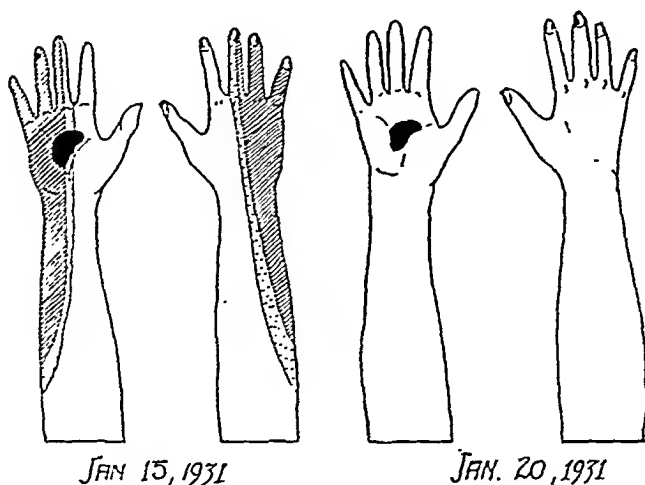


Fig. 1 (case 1).—Chart of sensory changes in the right hand. Note the relation of the wound at the center of the area of hyperalgesia to the sensory loss. Note also the fact that the sensory loss does not correspond to the distribution of the peripheral nerves. Complete return of sensation is indicated four days after a short period of fever. The shaded areas indicate marked hypesthesia and hyperalgesia; the stippled areas indicate moderate hypesthesia and hyperalgesia; the black areas indicate hyperalgesia.

on Jan. 13, 1931, with the diagnosis of a vasospastic state following trauma and infection.

A general examination made at this time revealed no abnormalities. Local examination showed markedly decreased power in the right hand, especially in the third and fourth fingers, with a healed scar in the palm of the hand. The patient held the third, fourth and fifth fingers in semiflexion. Sensory changes, which were unanatomic, are shown in figure 1. The hand was bluish, cold and moist. There was some atrophy of the subcutaneous tissues and skin. The flexor muscles of the forearm were in moderate spasm, particularly on the ulnar side, suggesting the "reflex spasm" of Weir Mitchell.

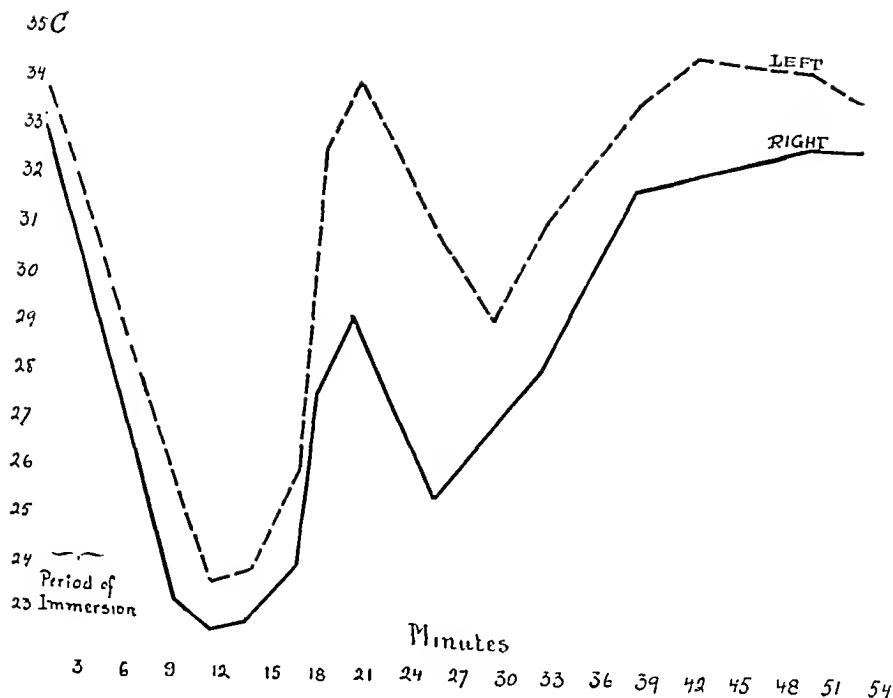


Fig. 2 (case 1).—Curve for surface temperature of the hands following immersion for three minutes in water at 0 C. There is a marked delay of the diseased hand in reaching the control temperature. Compare with figure 4.

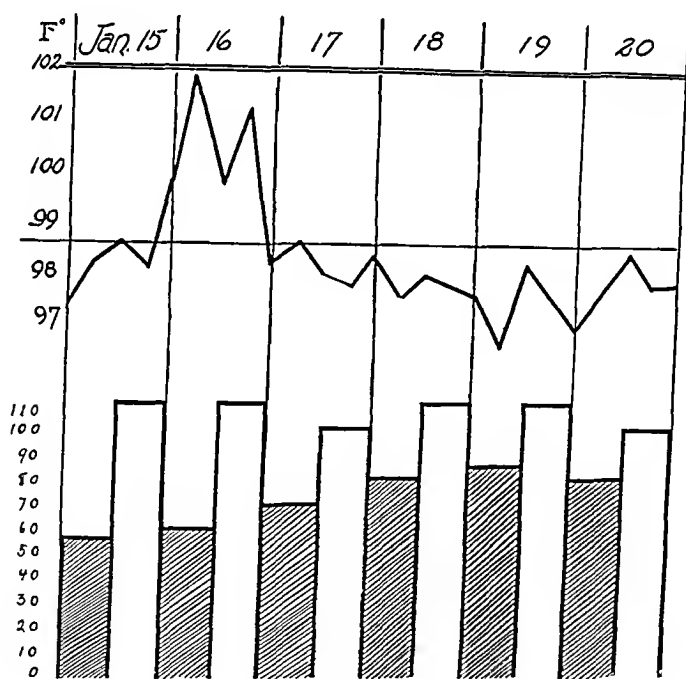


Fig. 3 (case 1).—This chart illustrates the progressive increase in strength of the diseased hand during six successive days. On January 15 typhoid vaccine was given, and on January 16 the patient had an infection of the upper respiratory tract with fever. From that date on strength increased from 55 to 80 per cent of normal. The upper graph shows the oral temperature; the shaded areas indicate the ergometer readings on the diseased hand; the white areas, the readings on the normal hand.

On Jan. 15, 1931, the surface temperature reactions to immersion in ice-water for three minutes were studied (fig. 2). There was a slower return of the surface temperature to the usual level in the involved as compared to the opposite hand. The exposure to cold water caused extreme pain. The hand returned to its previous level of surface temperature in about one hour.

Fifteen minutes later mixed typhoid vaccine, 25,000,000 organisms, was given intravenously. There was no effect on the body temperature. One hour and thirty minutes after the injection the grip in the right hand suddenly became approximately normal in strength; movements became free, and the hand became flushed. This curious reaction disappeared in fifteen minutes, and the hand returned to its previous condition.

The following day an acute cold with a rise in temperature to a maximum of 101.8 F. developed. The fever lasted twenty-four hours (fig. 3). From the onset

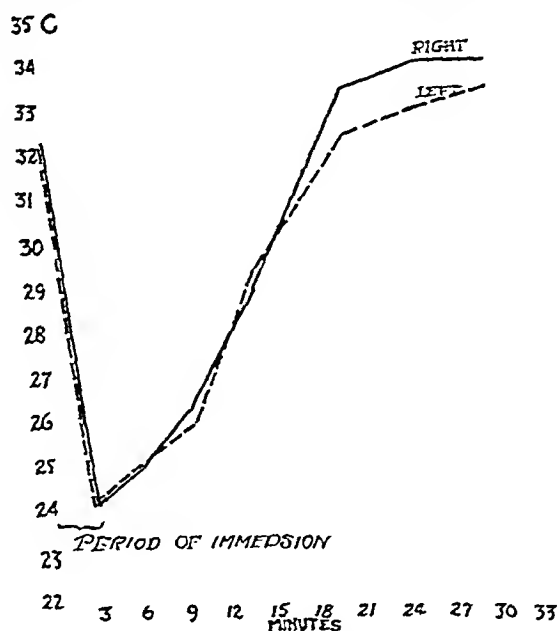


Fig. 4 (case 1).—Response of the two hands to immersion in ice-water four days after the fever. Compare with figure 2. The curves are now almost identical. On this date (Jan. 20, 1931), sensory changes had disappeared, and strength had risen from 55 to 80 per cent of normal.

of this fever the patient's hand began to improve. The grip increased; the color became pink, and the neurologic changes disappeared.

An ordinary grip ergometer was first used on the day of the injection of typhoid vaccine. A progressive increase of strength in the hand is shown, as illustrated by the diagram superimposed on the temperature curve (fig. 3). The residual defect of 20 points, shown four days later, may perhaps be ascribed to the atrophy of disuse.

Four days after the onset of the fever the surface temperature of the two hands was equal, and the test with ice-water showed equally prompt reactions (fig. 4). On this occasion no pain was caused by exposure to cold. A third test

six days after the second showed a similar curve. A sensory examination four days after the fever showed the hand to be normal, except for a slight hyperesthesia around the scar (fig. 1).

The patient was discharged from the hospital two weeks after admission with an apparently normal hand except for a slight weakness of the grip. On March 6, 1933, over two years following treatment, he wrote: "My hand is all right except the little finger. In cold weather it bothers me some."

The patient was seen in June, 1933. An examination showed equal and excellent power in the two hands and no differences in color, moisture or surface temperature. The little finger tends to become numb on cold mornings. The patient is capable of continuous hard manual labor and has been so since his discharge from the hospital.

This patient had a loss of motor function, unanatomic hypesthesia, coolness, blueness and moistness of the right hand, lasting nearly five months. The vasospasm was temporarily released following an injection of typhoid vaccine which gave no primary constitutional reaction and permanently released after a fever of twenty-four hours' duration. With the release of vasospasm, motor power promptly returned and clearcut unanatomic sensory changes disappeared. At the outset the neurologist who saw this patient in consultation inclined to a diagnosis of hysteria. It is hardly probable, however, that the objective records of response of surface temperature to cold could be so logically produced by hysteria. Further comment on this point is made subsequently. It must be noted in passing that an earlier diagnosis would have saved this man nearly five months of pain and uselessness and his insurance company a considerable sum of money.

*CASE 2.—Injury to palm with tendon division and immediate suture. Unsatisfactory tendon healing. Slight vasospasm. Loss of motor power in adductors of thumb. Spastic state of flexor muscles of forearm. Unanatomic hypesthesia of finger. Artificial fever induced. Strength of thumb adductors nearly tripled. Flexor spasm released. Reaction to cold improved. Patient still under treatment.*

W. E. T., a right-handed white farmer, aged 46, was first seen in the outpatient department on Jan. 3, 1933, with an incised wound of the distal portion of the palm of the left hand, severing the flexor tendons to the middle finger. The interphalangeal joints of the first finger were ankylosed from an old injury. A longitudinal incision was made over the course of the tendons which were sutured. The wounds healed cleanly. When last seen in the outpatient department on Jan. 28, 1933, it was noted that there was practically no motion in the middle finger.

I first saw the patient on March 8, 1933. At the time he was complaining of almost complete disability of the left hand, without pain. An examination showed the scar of the operation and the scar of the original injury (fig. 5). The hand was slightly blue, cool and moist as compared to the right hand. There was no difference in the radial pulses. Extension at the metacarpophalangeal joints of the hand was limited by about 15 degrees. Flexion at this joint was possible to almost a normal amount. In the forefinger motion was limited by the old ankylosis. In the middle finger there was no flexion at the distal joint, suggesting proba-

ble separation of the suture line of the deep tendon, or possibly fusion of the tendons. There was great weakness of the adductors of the thumb with atrophy in this area. There was hypesthesia to pin-prick over a portion of the palmar surface of the middle finger (fig. 5).

In addition to the abnormality in the tendons it was felt that this patient presented evidence of traumatic vasospasm, and he was admitted to the hospital for study.

Immersion of the two hands in ice-water showed a marked delay in the return of surface temperature in the left hand (fig. 6). An ergometer devised by the department of physiology for measuring the strength of the adductors of the thumb showed that on the left side these muscles had 20 per cent of the strength of the corresponding muscles on the right side (fig. 7). The patient was then given 50,000,000 killed typhoid bacilli intravenously, with a slight rise in the body temperature (fig. 7). During the course of this slight fever the strength of the adductors was almost doubled. The following day a similar dose of 75,000,000

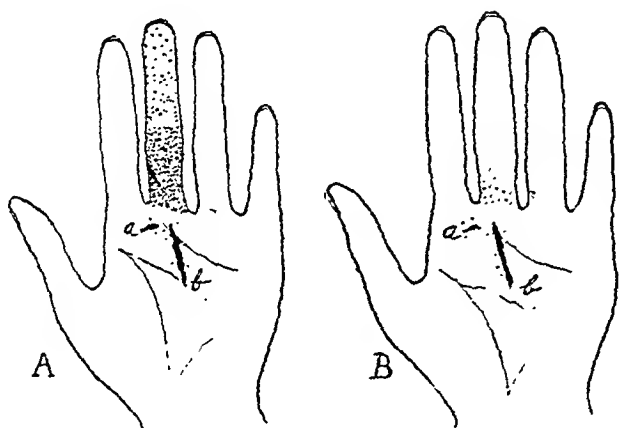


Fig. 5 (case 2).—A, sensory loss preceding, and B, following, induced fever. Note the unanatomic distribution of sensory loss and its almost complete disappearance three days later, following the induced fever. Note that neither the accidental, *a*, nor the surgical wound, *b*, could involve the motor fibers to the adductors of the thumb. The degree of hypesthesia is shown by the intensity of the stippling.

organisms was given (fig. 7), following which there was a chill and a maximum oral temperature of 103.4 F. During the course of this fever the strength of the adductors went up from  $1\frac{1}{2}$  pounds (0.7 Kg.) to  $2\frac{3}{4}$  pounds (1.2 Kg.), almost triple the strength of these muscles on admission. The morning after this fever, when the temperature was again approximately normal, a remarkable change was observed in the hand. The hypesthesia of the finger had almost completely disappeared (fig. 5), and the limitation of extension was gone. The latter had at first been thought to be due to a contraction of scar tissue, but this observation showed definitely that its origin lay in muscular spasm in the forearm or hand which was released by sympathetic paralysis. In addition the response of the surface temperature to immersion of the hands in ice-water showed a definite approximation of the curve for the diseased side to that of the normal side (fig. 8). The strength of the adductors had returned almost to the original level (fig. 7).



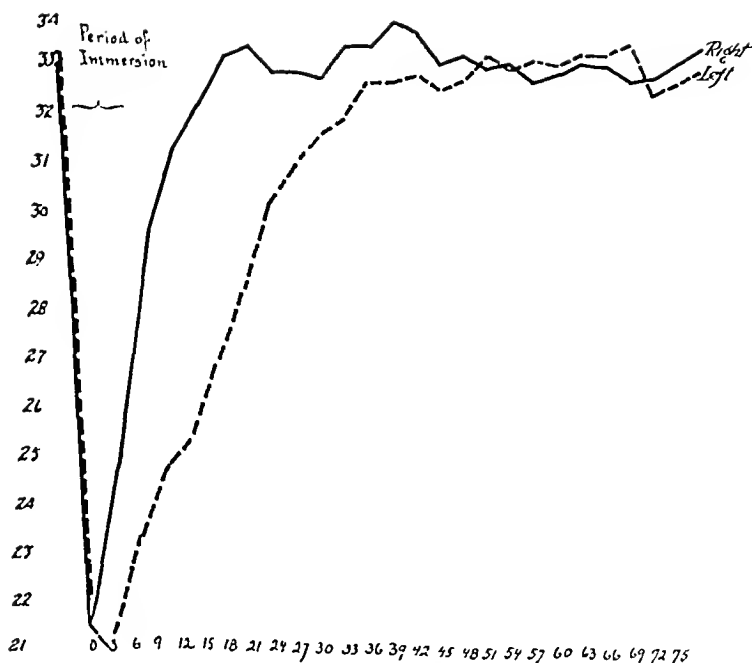


Fig. 6 (case 2).—Curve for surface temperature of fingers of the right and left hands, following immersion for four minutes in water at 0 C. The diseased hand does not reach the control level for over forty-five minutes; the normal hand does so in fifteen minutes (March 9, 1933). Compare with figure 8.

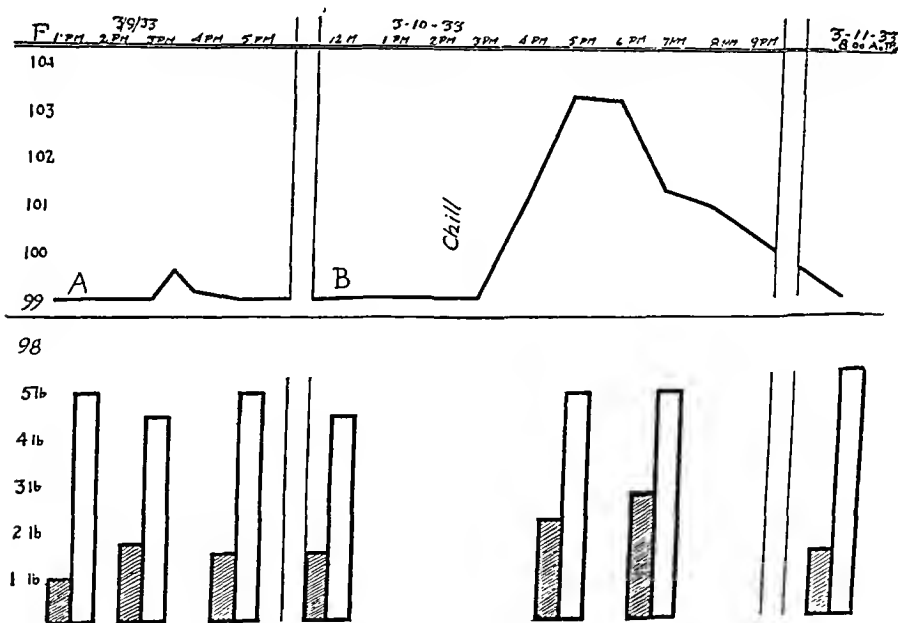


Fig. 7 (case 2).—Ergometer readings (thumb adductors) plotted against oral temperature in induced fever. Note that with the slight rise in temperature on March 9 the pull of these muscles is increased 75 per cent and that at the height of the fever on the next day it is increased 175 per cent. On the third day it remains 50 per cent above the original level. *A*, chart for temperature following intravenous inoculation with 50,000,000 typhoid bacilli. *B*, chart for temperature following inoculation with 75,000,000 typhoid bacilli. The shaded areas represent the ergometer readings for the diseased hand; the white areas, the readings for the normal hand.

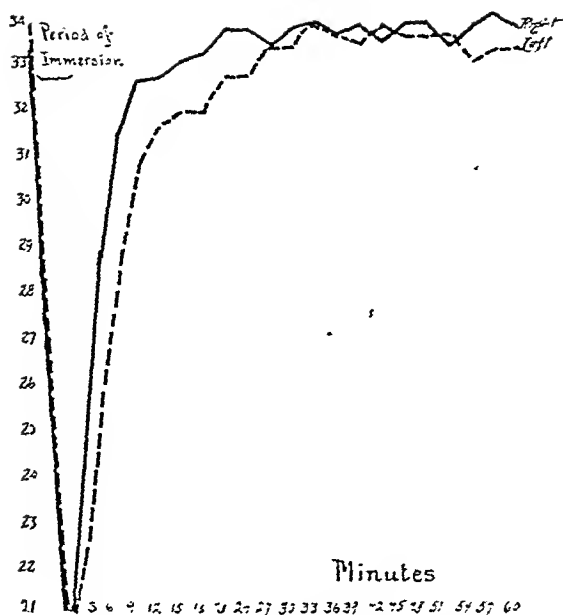


Fig. 8 (case 2).—Curve for surface temperature of the fingers of the right and left hands following immersion for four minutes in water at 0 C. These readings were made twenty-four hours after a rise in temperature following inoculation with typhoid vaccine. Note that the curve for the diseased hand approaches that for the normal hand on the day following the induced fever (March 11, 1933). Compare with figure 6.

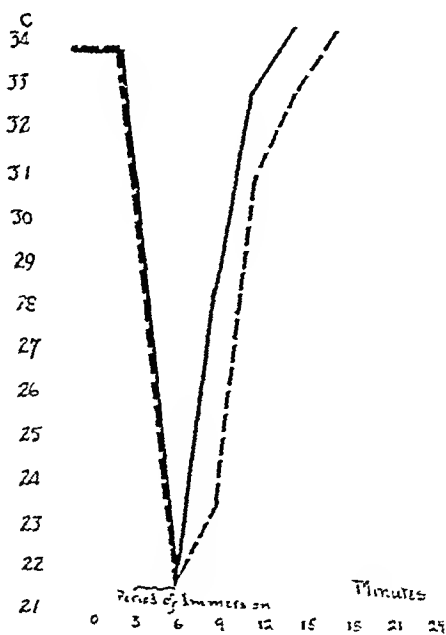


Fig. 9 (case 2).—Curve for surface temperature of finger of the right and left hands following immersion for three minutes in water at 0 C. This test was made two months after that shown in figure 8.

The patient was discharged from the hospital and instructed to return for physical therapy, consisting of massage and diathermy. He was to report for further study and decision on exploration of the tendons.

Nearly two months later after many efforts, the patient was brought back to the hospital. An examination showed no further evidence of the changes which had been observed on his first admission, except that the forefinger and the middle finger were in the original condition. The hand was no longer blue, moist or cool, there were no sensory changes, and the strength of the adductors was equal to that of the adductors of the normal hand. Atrophy was completely absent; the thenar eminences were equal in volume. As softening of the operative scar permitted more adequate palpation, it appeared likely that the tendons were tied up in scar tissue rather than separated. A chart of the reactions to cold water was obtained (fig. 9), showing still a slight delay in the return of surface temperature on the involved side.

The most striking observation at this time was that the patient found his hand entirely useful and did not want to consider the problem of operation on the tendons. In other words, the most disabling portion of his disturbance in function was the portion resulting from vasospasm, in spite of the fact that the flexion of one finger was entirely lost. Unquestionably a part of the explanation for this phenomenon lay in the fact that he had previously accustomed himself to an ankylosed forefinger so that the additional loss of flexion of the adjoining finger was relatively unnoticed.

When the patient was seen last on June 16, 1933, there was beginning subluxation at the proximal interphalangeal joint, owing unquestionably to the pull of the interossei. It is probable that the patient should now have exploration of the tendons, although I should be disposed to repeat the artificial fever once more before operating, in view of the recent reaction to cold.

There is little doubt that this case represents a degree of sympathetic irritation, with vasospasm and sensory and motor disturbances comparable to those seen in case 1. The time of onset of the sympathetic symptoms is not clear. The question may be raised as to whether disturbances in healing of the tendon after suture may not have been due to early circulatory disturbance from this underlying sympathetic malfunction. Certainly it seemed meddlesome to attempt ordinary reparative surgical procedures on this crippled hand until all evidence of sympathetic disturbance had been removed. The degree to which sympathetic dysfunction alone can cripple an extremity is particularly emphasized by this case. The hand was useless to the patient while vasospasm was present and became entirely useful when vasospasm was absent, in spite of the fact that two fingers remained without flexion at the interphalangeal joints.

*CASE 3.—Superficial puncture wound of the elbow. One month later, increasing awkwardness and weakness of the hand with sensation of coolness. Hand objectively pale and cool. No vasomotor studies. Excision of chronic inflammatory nodule over olecranon. Complete relief of symptoms. Pathologic report: chronic inflammation with perivascular infiltration.*

In A. R. P., an unusually intelligent and well educated white woman, aged 45, a rose thorn penetrated the right elbow just below the olecranon. An immediate

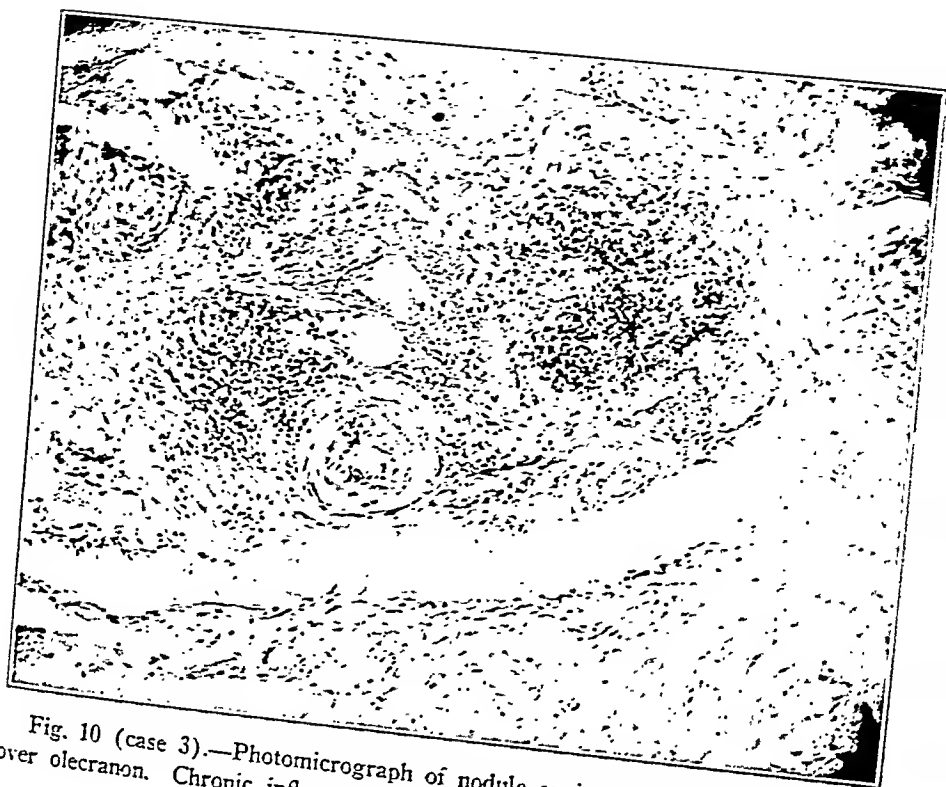


Fig. 10 (case 3).—Photomicrograph of nodule excised from superficial tissues over olecranon. Chronic inflammation and perivascular infiltration.

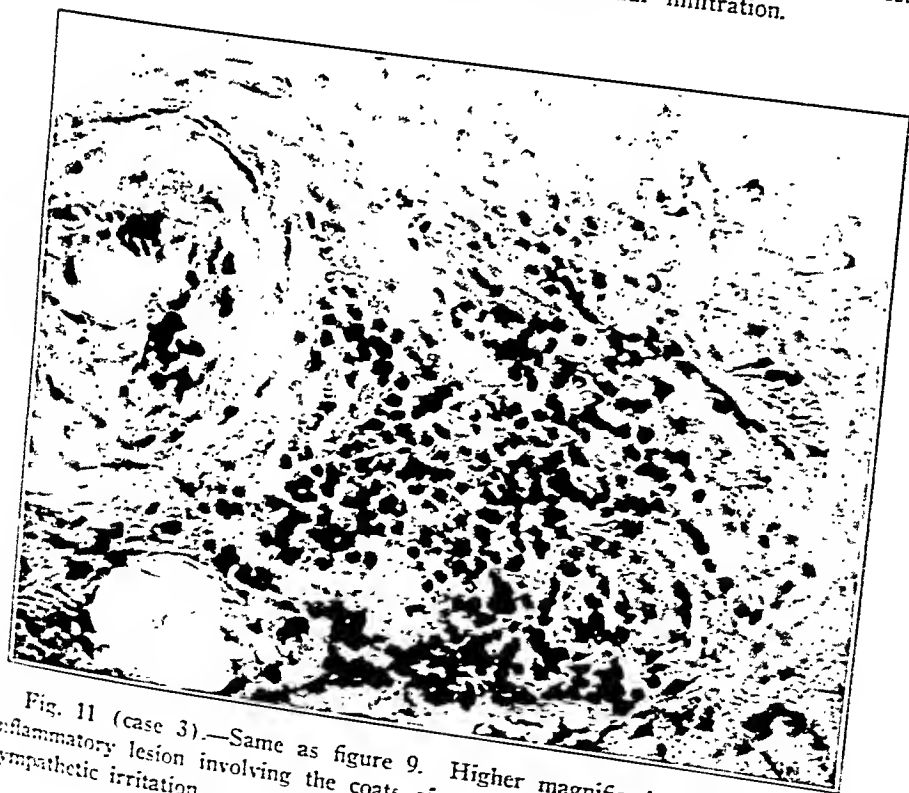


Fig. 11 (case 3).—Same as figure 9. Higher magnification to demonstrate inflammatory lesion involving the coats of a small artery, a possible source of sympathetic irritation.

unsuccessful search for a foreign body in the skin was made by a physician, with the aid of a lens. The spot of entrance of the thorn remained tender, and a nodule developed.

The patient was a successful author who set herself a regular task of composition for four hours daily. She was right-handed and did not employ the typewriter or dictation. She was seen about four weeks after the injury.

Recently the hand had not felt normal. It had been somewhat awkward and had tired easily. It felt cold. The patient expressed it by saying "it feels as though the circulation is not right."

The examination showed at the point of injury, a small, slightly tender black dot in the skin that could barely be seen. Underlying this was a nodule about 3 mm. in diameter. There was no redness or heat. The right hand was slightly paler and cooler than the left. No objective observations as to surface temperature were made.

A diagnosis of sympathetic vasospasm from perivascular irritation from a foreign body was thought possible, and excision of the nodule was advised.

Under local anesthesia the nodule was excised down to the deep fascia including surrounding fat. A small artery was demonstrated entering the area of inflammatory tissue. This observation is of interest in relation to the possibility of disturbance of the sympathetic nervous system.

The wound healed cleanly. There was practically immediate return of normal sensation and function in the hand and arm, which has remained normal since. The pathologic diagnosis was: "section of skin showing chronic inflammation, perivascular infiltration and vacuolization" (figs. 10 and 11). No foreign body was present.

This case shows in a very minor degree the elements that one must recognize as being present in major degree in the other cases detailed. There is no proof that this relatively slight disturbance is sympathetic in origin or that it may not be entirely explained on a psychic basis. The sequence, however, of injury in the neighborhood of a vessel, coolness and dysfunction in the extremity, pathologic demonstration of perivascular inflammation, and immediate complete disappearance of symptoms following removal of the limited area in which the inflammation is present, is logical and orderly to a degree. If one assumes, then, that this case represents a slightly developed instance of the conditions under discussion, it has particular interest from several points of view. In the first place, the condition was diagnosed and successfully treated at an exceedingly early stage. In the second place, the treatment was unusual in that the focus of sympathetic irritation could be completely ablated. In the third place, the pathologic picture of changes that may produce sympathetic irritation is furnished for study. Lastly, these pathologic changes are strikingly similar to those in the case of sympathetic malfunction about to be presented.

CASE 4.—*Puncture wound of right forearm. Twelve months of treatment as infection. Complete disability of upper arm, forearm and hand. Continuous pain. Marked doughy swelling. Coolness. Amputation considered. Brachial periarterial sympathectomy. Cure.*

D. E. D., a white schoolgirl, aged 18, first entered the hospital on Feb. 27, 1929, complaining of a painful, useless right hand following a wound in the right forearm. Four months previously a crabapple thorn had penetrated the ulnar border of the right forearm. Two days later the whole forearm became red, swollen and painful. She had had several incisions with the placing of drains after pus was obtained.

On admission the following description of her condition was made: "The lower part of the right arm is held by the left hand for fear of hurting it. The patient can move the right wrist only a little, can move the fingers only with difficulty and has no grip in the right hand. The arm cannot be pronated. There is a small draining sinus in the forearm in the middle third from which whitish pus exudes. There are induration, swelling, redness, tenderness and local heat surrounding the sinus as well as halfway to the elbow and wrist. The sinus leads down to the ulna, but no bare bone was made out. No epitrochlear or axillary glands were felt."

A diagnosis of retained foreign body was made, and at operation two small wooden splinters were removed. A roentgenogram showed no evidence of destruction of the bone. The patient was discharged on March 3, 1929, and was readmitted on June 10, 1929. The wound of the previous operation had healed. Two months later the arm began to turn red, to swell and to become painful at the original site. The wound broke open and suppurated. On June 13, 1929, another operation for drainage was performed, but no foreign body was found, and the patient was discharged on June 16.

On July 13, she was readmitted without any permanent improvement. There had been improvement for a time, but the incisions did not heal. Later the arm again became swollen and painful. It was noted at this time that the discharge from the wound was bloody serum and not pus. An examination showed bluish discoloration of the skin surrounding the two incisions with swelling and tenderness in the forearm in this region. A note stated: "The patient cannot flex the wrist or fingers of the right hand. The right arm is lifted with effort and pain." It is notable that at this time her temperature and leukocyte count were normal. The stiffness of the right wrist and hand was ascribed to disuse.

Persistence of the idea that the continued inflammation and disability were due to a retained foreign body led to a third operation on July 20. At this time the sinus tracts were laid wide open and dissected. No improvement followed, in spite of continuous applications of wet heat, diathermy, massage, roentgen treatment and finally the application of a cast.

On August 26, another area of redness and swelling developed; this was excised. Microscopic study showed inflammation in the fat tissue, including particularly perivascular infiltration (fig. 12). The pathologic changes in this lesion were strikingly similar to those described for case 3 (figs. 10 and 11), although not different from those found in many areas of chronic inflammation. The patient was discharged on September 3, apparently slightly relieved.

She was readmitted on September 25, and I was asked to see her. The disability in the arm had become practically complete. Pain was almost continuous, requiring the use of sedatives. The arm was held flexed at an angle of 90 degrees.

The forearm was definitely tender over its entire surface. The forearm and upper part of the arm to a point  $\frac{1}{2}$  inch (1.2 cm.) below the border of the axilla were swollen and doughy. Two of the old incisions were healed, and one was only partially healed. The right radial and brachial arteries were less easily felt than the left. The fingers were somewhat cool.

At this time the leukocyte count was 8,720 with 65 per cent polymorphonuclear leukocytes. All the other examinations including roentgen study of the right arm failed to reveal any abnormalities. No objective measurements of surface temperature or other special studies were made.

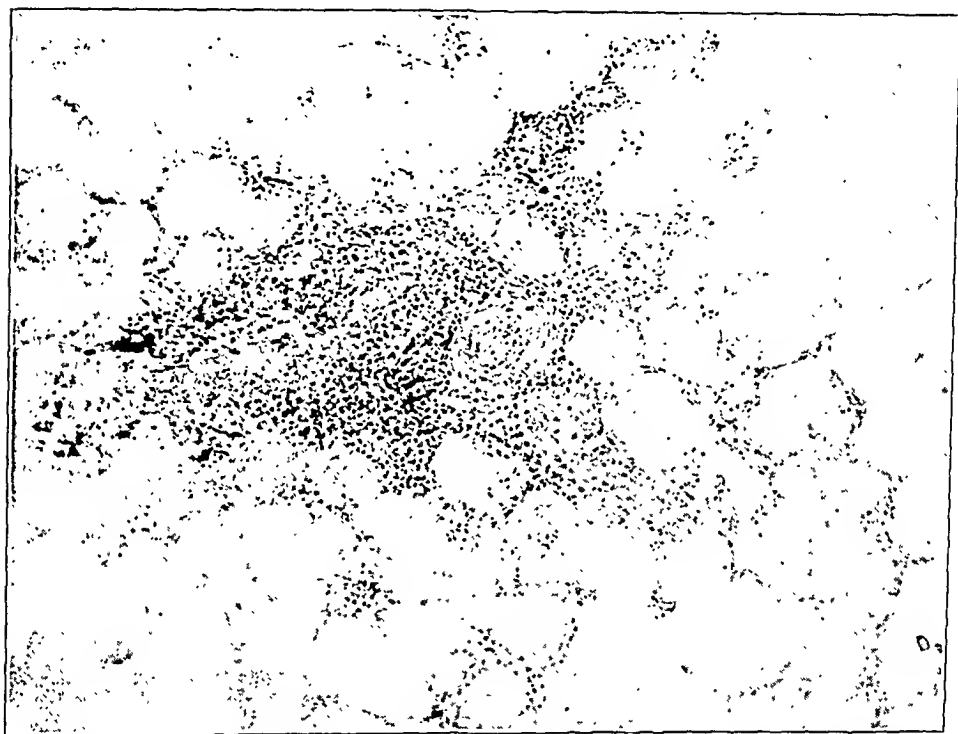


Fig. 12 (case 4).—Photomicrograph of tissue removed at the fourth operation, Aug. 26, 1929. Chronic inflammation and perivascular infiltration. The lesion resembles closely that seen in case 3, figures 10 and 11.

Before I was asked to see the patient it had been felt that the condition was hopeless and that she deserved the relief from intense suffering that amputation would offer. The condition, however, was suggestive of the rather ill defined state which was observed in injuries received in the war and called trophic edema. This was usually seen following small penetrating wounds of the type described. Certainly the choice seemed to lie between amputation and sympathectomy.

On September 28, therefore, a periarterial sympathectomy was performed on the right brachial artery with the typical primary and secondary physiologic results. The postoperative course and the healing of the wound were normal.

On September 30, the following note was made: "Patient now seems to have much better movement of the fingers than before the operation. The arm is not so tender." On October 15, the following note was made: "Flexion at elbow normal, extension to 120 degrees. Palmar and dorsal flexion of hand to about 15

degrees. The wound is healed." The hand which had been warm and dry from the time of the operation to about this date began to approach the temperature of the normal hand. The measurements of swelling before and after the operation showed an average diminution of from 1 to 2 cm. in the circumference of the arm in ten days. The patient was discharged on October 15.

She has been followed by letter and by a single visit. Improvement, begun before she left the hospital, was uninterrupted. On March 14, 1930, five and one-half months after the operation, her father wrote that the wound had healed and the hardness of the arm had disappeared, but that there was still some weakness of the fingers. On March 19, her physician wrote that the movements of the hand and arm were normal, that there was no pain, and that she was able to use the arm actively in housework, the only abnormality being the scars from earlier operations. The patient reported in person on June 14, 1932, two years and nine months after the operation. No abnormality was found except the scars, one of which was slightly attached to the ulna. The surface temperatures of the hands were equal.

This case is illustrative of two points: first, the serious loss in suffering and expense, running through an entire year, that resulted from failure to recognize the condition, and, second, the present lack of a clearcut conception of the disease from a lack of proper study before operation on the sympathetic nerves. The former needs no comment. The latter must be strongly emphasized. I have named the condition somewhat hesitantly "trophic edema." It is not at all improbable that adequate study would have enabled me to diagnose it with certainty and probably to have placed it in the group just presented, namely, that of vasospastic states following trauma. Finally, attention must again be called to the pathologic picture presented here and in the preceding case. Perivascular cellular infiltration was an outstanding element in both, furnishing an obvious mechanism for the irritation of sympathetic fibers.

This presentation illustrates several points of importance. In the first place it indicates how much information can be gained by a properly complete study of these unusual phenomena. With earlier cases, including the instance of trophic edema here reported, an adequate study of the sympathetic function of the extremity was not carried out. One can never hope to understand the curious sensory and motor effects that may be seen in disabilities of presumed sympathetic origin until in a long series of cases one can look back at objective records and detect some uniformity of behavior in relation to the supposed etiology of the condition and to the various forms of treatment exhibited. Only through the careful study of the first case here presented was a recognition of the two similar cases made possible.

The second point of importance is the recording, in as great a number as possible, of these curious states illuminated by modern methods of study and treatment, in order that they may be recognized by all practitioners in early stages. There is no doubt that in my own experience



in earlier years, a number of patients have been allowed to suffer or recover slowly without the benefit of a proper diagnosis. It is noteworthy that the case of trophic edema herein presented was called to my attention with the suggestion that amputation was indicated. This patient had had more than adequate treatment by ordinary means, faithfully followed out, with no improvement whatever. Today she is well, with an entirely useful arm which might easily have been sacrificed four years ago.

One case presented suggests the possible relationship between these states and the healing of wounds. It is essential that all physicians treating accidental wounds be on the alert for vasospastic phenomena which may come on slowly following an injury. The cool, blue, moist, perhaps painful, usually somewhat disabled hand is the danger signal. One must not be content with such expressions as the atrophy of disuse or splint stiffness until one is convinced that sympathetic impulses are not at fault.

The diagnosis of these sympathetic disturbances is not necessarily difficult, provided the sympathetic system is kept in mind. Differentiation from traumatic neurosis and hysteria is another matter. I am not entirely satisfied that in at least two of these cases the psychic factor has received sufficient attention. If anything is meant by traumatic vasospasm, however, it is probable that these cases should be so classified. One must remember that what is now called by this name was included by the earlier writers under the blanket term of vasomotor neurosis. There is, of course, a psychic element in every injury and disease. Recent studies of surface temperature reactions by the newer methods have demonstrated more and more clearly the great sensitiveness of vasomotor control to emotional stimuli. It may well be that the psychic factor is predominant in any instance of traumatic vasospasm. Looked at from this point of view the importance of differentiation between this condition and a pure hysterical reaction diminishes greatly. If traumatic vasospasm can be recognized as an entity and can be relieved by medical or surgical measures directed toward the sympathetic control of the blood supply to the extremity, the psychic element need have no more attention than the psychic element in any sick person.

It becomes necessary, therefore, only to show that a vasospastic element is present. In most instances the objective tests, which have been illustrated in the cases presented, are sufficient to accomplish this. The effect of cold on the volume flow of blood, as measured by the curve for surface temperature following immersion in ice-water, is of great value. The reaction of surface temperature and the response of symptoms to methods reducing sympathetic activity are of equal value. In the type of lesion under discussion the production of an artificial fever by typhoid vaccine is, to my mind, the method of choice. Blocking of

the sympathetic pathways by injection of procaine hydrochloride at any level will teach nothing about the relief from pain, recovery of sensory loss or improvement in somatic motor function. Its usefulness is limited to a demonstration of its effect on volume flow and sweating. Artificial fever, however, as has been illustrated herein, may furnish information of tremendous importance not only as regards the volume flow of blood but also in the field of symptomatic changes. In addition, in certain cases vasospasm can apparently be permanently released and the condition cured by artificial fever. One must, of course, be on the alert for the *post hoc* fallacy.

Lastly, the methods of treatment of the individual patient must be individualized. With methods now available, there is little doubt that in the conditions under consideration at least one or two treatments with typhoid vaccine should be tried before surgical measures are instituted. How individual the treatment may be is illustrated by case 3, in which the excision of a small superficial inflammatory nodule was all that was needed. As these cases illustrate, one is not justified in advising surgical intervention on the sympathetic system simply because the diagnosis of sympathetic disturbance has been made.

# NEUROFIBROMATOSIS WITH OCULAR CHANGES AND INVOLVEMENT OF THE THORACIC SPINE

REPORT OF A CASE

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Pigmentation of the skin and multiple neurofibromas are characteristic of Recklinghausen's disease, but numerous other manifestations are seen.<sup>1</sup>

Changes in the bone have been observed in cases of neurofibromatosis. Brooks and Lehman,<sup>2</sup> Castronuovo,<sup>3</sup> Camp,<sup>4</sup> Camp, Adson and Shugrue,<sup>5</sup> Gould,<sup>6</sup> Weiss,<sup>7</sup> Adrian,<sup>8</sup> and Stalmann<sup>9</sup> reported cases with various associated changes in the bone, including scoliosis, abnormality of growth, irregularity of outline, central and subperiosteal cysts, pedunculated subperiosteal tumors and pseudo-arthritis.

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From the Memorial Hospital.

1. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, *Am. J. Cancer* **15**:1235, 1931.

2. Brooks, B., and Lehman, E. P.: The Bone Changes in Recklinghausen's Neurofibromatosis, *Surg., Gynec. & Obst.* **38**:587, 1924.

3. Castronuovo, G.: Diffuse Neurofibromatosis (von Recklinghausen's Disease), *Riforma med.* **36**:817, 1920.

4. Camp, J. D.: A Roentgenologic Study of Osseous Changes with Neurofibroma of the Spinal Cord and Associated Nerves, *Proc. Staff Meet., Mayo Clin.* **8**:239, 1933.

5. Camp, J. D.; Adson, A. W., and Shugrue, J. J.: Roentgenographic Findings Associated with Tumors of the Spinal Column, Spinal Cord and Associated Tissues, *Am. J. Cancer* **17**:348, 1933.

6. Gould, E. P.: The Bone Changes Occurring in von Recklinghausen's Disease, *Quart. J. Med.* **11**:221, 1918.

7. Weiss, R. S.: XVIII. (A) Von Recklinghausen's Disease in the Negro (B) Curvature of Spine in von Recklinghausen's Disease, *Arch. Dermat. & Syph.* **3**:144 (Feb.) 1921.

8. Adrian, C.: Neurofibromatosis and Its Complications, *Beitr. z. klin. Chir.* **31**:1, 1901.

9. Stalmann, A.: Nerve, Skin and Bone Changes in Recklinghausen's Neurofibromatosis and Their Developmental Interrelationships, *Virchows Arch. f. path. Anat.* **289**:96, 1933.

Siegmund<sup>10</sup> reported a case of neurofibromatosis with bony cavities of the lumbar and sacral vertebrae lined by herniations of the dura and accompanied by aneurysmal dilatations of vertebral arteries.

Ocular changes associated with Recklinghausen's disease are also recorded. Goldstein and Wexler<sup>11</sup> described a case of melanotic tumors of the iris with orbital neurofibromas and called attention to the frequent occurrence of orbital neurofibromatosis accompanied by pigmented nevi of the lids, conjunctiva and sclera, hydrophthalmos, buphthalmos, elephantiasis of the lids and melanosis of the uveal tract and iris.

The following case presents features of Recklinghausen's disease with extensive medullation of the nerve fiber layer of the retinas and changes of the bone in the thoracic vertebrae.

#### REPORT OF A CASE

M. W., a Jewish youth, aged 14, was referred to the Memorial Hospital in March, 1933, by Dr. H. Hallock, of the Orthopedic Hospital, Orange, N. J., complaining of discomfort and deformity in the upper part of the back.

The patient's father had typical coffee-colored patches in the lower lumbar region. A paternal aunt had a similar spot over the right shoulder.

At birth the boy had what was called a large brown mole on the back. As he grew older, various pigmented areas appeared over the body. Development seemed to be normal in every other respect.

Two years before admission to the hospital he began to experience pain in the upper posterior thoracic region and lassitude, especially in the evening. One year later his mother noticed a deformity of the thoracic spine.

Physical examination on admission revealed a fairly well nourished youth.

A special examination of the eyes by Dr. A. B. Reese showed the palpebral apertures to be of equal size; the exophthalmometer reading was 19 mm. for each eye. No masses were palpable in the orbits. The lids were normal. The extraocular movements were normal. The pupils were equal and regular; they reacted to light and in accommodation both directly and consensually. Slit-lamp examination gave negative results. Ophthalmoscopic examination showed extensive medullation of the nerve fiber layer of the retina in both eyes. In the right eye the medullation completely surrounded the disks and extended into the retina for 2 disk diameters above and below, while temporally and nasally it extended only 1 disk diameter. In the left eye there was no medullation of the fiber layer temporally and nasally to the disk, but above and below it extended for 1 disk diameter. The examination of the fundus of the eyes with widely dilated pupils otherwise gave entirely negative results.

The fields of vision were taken on the Ferree-Rand perimeter under standard illumination with a 5 mm. test object. They were of normal limits. The blind spots, taken on the tangent screen with a 5 mm. test object, were normal.

There was slightly reduced vision in the right eye. This was attributed to amblyopia exanopsia, as the patient had considerable hyperopia and esophoria with a history of slight esotropia.

10. Siegmund: München. med. Wchnschr. 90:28, 1930.

11. Goldstein, I., and Wexler, D.: Melanosis Uvae and Melanoma of the Iris in Neurofibromatosis, Arch. Ophth. 3:288 (March) 1930.

The intra-oral cavity showed poor approximation of the teeth; otherwise it was normal. There was moderate adenopathy in the neck.

Examination of the chest showed a markedly keel-like thorax. There was a rotation of the upper thoracic vertebrae toward the right, and a displacement of the ribs backward on the right. Kyphosis and right scoliosis existed in this region. There was slight tenderness definitely localized over the upper dorsal vertebrae. An extensive area of pigmentation was found over the back (fig. 1). Several smaller areas of pigment covered the anterior part of the chest and arms.

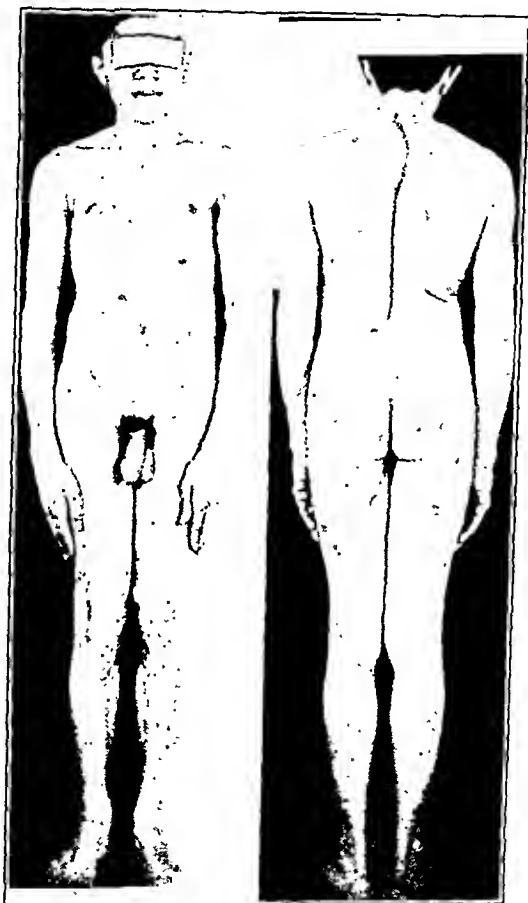


Fig. 1.—Note the extensive areas of pigmentation. The right scoliosis of the spine can be seen with displacement of the right scapula and ribs backward.

The heart and lungs were normal.

The abdomen also was covered with small areas of coffee-ground spots. The spleen was just palpable. No other masses were felt in the abdomen.

Examination of the genitalia showed pigmentation of the glans penis; the testes were normal. Rectal examination gave negative results.

On the lateral surface of the left hip, at about its midportion, was a small subcutaneous mass, suggesting a neurofibroma. The legs showed a wide distribution of Recklinghausen's pigment. No other subcutaneous masses were felt over the body.

Roentgenographic studies of the chest and spine showed marked right lateral scoliosis of the upper dorsal region. The bodies of the vertebrae in the scoliotic

region were wedge-shaped as a result of slight destruction, and the ribs in this vicinity showed multiple small areas of diminished density representing destruction of bone. All of these findings were in accord with the clinical diagnosis of neurofibromatosis.

The blood of the patient was studied for its intermedin content by Dr. Russell Ferguson. The intermedin was extracted from the blood and injected into Elritze fish (*Phoxinus laevis*), which were used as test objects. The blood was found to have 334 phoxinus units of intermedin per liter.

When last seen the patient showed no other changes clinically. He had been advised to refrain from strenuous exercise and was under close observation.



Fig. 2.—Roentgenogram showing right lateral scoliosis in the upper dorsal region. The bodies of the vertebrae are wedge-shaped as a result of slight destruction. The ribs in the vicinity show multiple areas of rarefaction due to changes in pressure.

#### COMMENT

Neurofibromas arise from spinal nerve roots as well as from the peripheral nerves. They may be intrameningeal or extrameningeal or extend along the course of the nerve. The extrameningeal portion may erode through the intervertebral foramen to form extravertebral masses. In the region of the thorax and abdomen they usually produce massive erosion of all of the adjacent bony structures.

Camp<sup>4</sup> of the Mayo Clinic found that between the years 1930 and 1932, inclusive, 23 per cent of all tumors of the spinal cord operated on were neurofibromas. He also found that 42 per cent of the cases showed osseous changes.

The bone is involved usually by direct pressure from erosion, and the defect observed in roentgenograms coincides with the site of the tumor. The roentgenographic changes are usually erosion and thinning of the vertebrae and their processes. Change in the contour of the vertebrae is a late manifestation. As the tumor increases in size, evidence of erosion of the ribs is seen. The discovery of a tumor extending along nerve roots and penetrating through the intervertebral foramina causing changes of the bone in this area should suggest the presence of a neurofibroma.

Medullated nerve fibers occurring in the retina have been found in cases of Recklinghausen's disease. In a study of 12 patients with neurofibromatosis, Fischer<sup>12</sup> found retinal medullated nerve fibers 4 times. He is inclined to the view that the incidence of medullated nerve fibers in the retina is greater among patients who show definite abnormalities in the central nervous system or have psychopathic disturbances. In a routine examination of the eyes of 3,250 patients Manz<sup>13</sup> found 1 patient with medullated retinal nerve fibers, while in an examination of 130 inmates of an asylum he found its occurrence 4 times.

The retinal medullated nerve fibers appear normal histologically when compared with medullated fibers<sup>12</sup> in nerves usually containing them.

In a personal communication Ferguson<sup>14</sup> stated that intermedin (the melanophore-expanding hormone of the pituitary) was found in the blood in 8 proved cases of melanoma and 1 case of neurogenic sarcoma besides our case of Recklinghausen's disease. He feels that it may be possible to find a fundamental relationship on a quantitative basis between melanoma, neurogenic sarcoma and neurofibromatosis. Such a finding would lend biologic support to Masson's theory and help exclude from this relationship tumors which do not arise from the chromatophore cells of the nerve sheaths or end-organs.

This case emphasizes the vertebral changes and ocular findings which may be associated with neurofibromatosis. The finding of intermedin in the blood is of interest and may lend biologic support to Masson's theory of the association of the chromatophore cell in the nerve sheaths and end-organs with Recklinghausen's disease.

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12. Fischer, H.: Contributions to Recklinghausen's Disease; Anomalies of the Eye, Particularly the Medullary Nerve Fibers of the Retina, *Dermat. Ztschr.* **42**: 143, 1924-1925.

13. Manz, quoted by Fischer.<sup>12</sup>

14. Ferguson, R. S., and Hilderbrand, G. E.: Preliminary Note on the Occurrence of Intermedin in Melanoma and Related Conditions, *Am. J. Cancer*, to be published.

# RETROPERITONEAL PERIRENAL LYMPHANGIOMA

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The retroperitoneal tissues above and below the kidney may be the seat of a variety of tumors, which may be benign or malignant, cystic or solid. It is generally assumed that benign tumors and cysts occur more frequently than do malignant growths, and that solid tumors are more commonly seen than the cystic type.

Gobell (1901) collected reports from the literature of 101 cases of retroperitoneal tumors, which he divided into the following groups:

	Cases
Benign retroperitoneal growths.....	43
Malignant retroperitoneal growths.....	32
Either type of retroperitoneal growths.....	14
Retroperitoneal cysts .....	12
	<hr/>
	101

No case of retroperitoneal lymphangioma is found in Gobell's collection of cases.

Maclaure (1910) studied tumors of the retroperitoneal space and described about the same varieties as Gobell did. Magoun (1919) reported a series of 73 retroperitoneal tumors, 53 of which were operated on, 29 proving malignant, while 18 were benign; the nature of 6 was not determined. Having recently had the opportunity of studying a rare type of retroperitoneal tumor we report the following case:

## REPORT OF A CASE

*History.*—Mrs. J. W., aged 59, referred by Dr. R. C. Brown, was admitted to the Presbyterian Hospital on Oct. 14, 1928. The patient gave a history of nocturia and mild frequency about eight years before admission. Since then she had had an ache in the right upper quadrant of the abdomen. Various physicians told her that she had an enlarged right lobe of the liver. She had never had jaundice or an acute pain in the right upper quadrant. For several years, she had felt a definite mass under the costal arch. When she was on her feet the mass felt heavy.

Read at the Annual Meeting of the American Association of Genito-Urinary Surgeons, Washington, D. C., May 10, 1933.



and dragged down somewhat. She had been told that she had liver trouble and had been placed on various dietary regimens.

For an indefinite period the patient had also felt a strain or ache or pulling in the right flank. Several weeks before admission she experienced a feeling of strain that ran down the right side, across the inguinal region to the groin and down the right leg on the medial side.

Urinary symptoms were absent, but the patient had been troubled with constipation.

*Physical Examination* (by Dr. R. C. Brown).—The head, neck, heart and lungs were normal. Examination of the abdomen revealed a firm, smooth, globular mass which almost filled the entire right upper quadrant, projecting down from



Fig. 1.—Roentgenogram of the right side, showing moderate hydronephrosis with marked dilatation and clubbing of the calices.

under the costal arch. The lower border was on a level with the umbilicus, extending almost to the midline. On deep palpation the mass moved down in such a way that it became readily palpable bimanually. Some tenderness was present over the lower pole of the mass. The liver, spleen and left kidney were not palpable. The genitalia were normal. Examination revealed normal reflexes.

*Laboratory Observations.*—A blood count showed: red blood cells, 5,130,000; leukocytes, 8,800, and hemoglobin, 84 per cent. The blood pressure was 124 systolic and 80 diastolic. Urinalysis showed 310 leukocytes per cubic millimeter of fluid from the bladder, 260 from the right kidney and none from the left kidney. Cultures were sterile, and inoculations of guinea-pigs gave negative results for tubercle bacilli. A roentgen examination on October 15 revealed no change in the bones and no calculi. A cholecystogram revealed a normal organ.

Cystoscopy disclosed a normal bladder. The left ureter was catheterized without difficulty or obstruction. On the right side the catheter met an obstruction about 2 cm. from the orifice, which was overcome with some difficulty.

A pyelogram of the right kidney showed moderate hydronephrosis, with marked dilatation and clubbing of the calices (fig. 1). A pyelogram of the left kidney showed it to be normal.

*Course.*—From the findings a diagnosis of tumor of the right kidney was made, and operation was advised.

Nephrectomy on the right side was done by one of us (H. L. K.) on October 26, with ethylene-ether anesthesia. There was an uneventful convalescence and the patient was discharged from the hospital on November 16.

*Examination of Specimen (W. G. H.).*—The gross specimen consisted of the upper and medial two thirds of the right kidney to which was attached, laterally and to its lower pole, a firm semispherical, encapsulated mass measuring 8.5 by 11 by

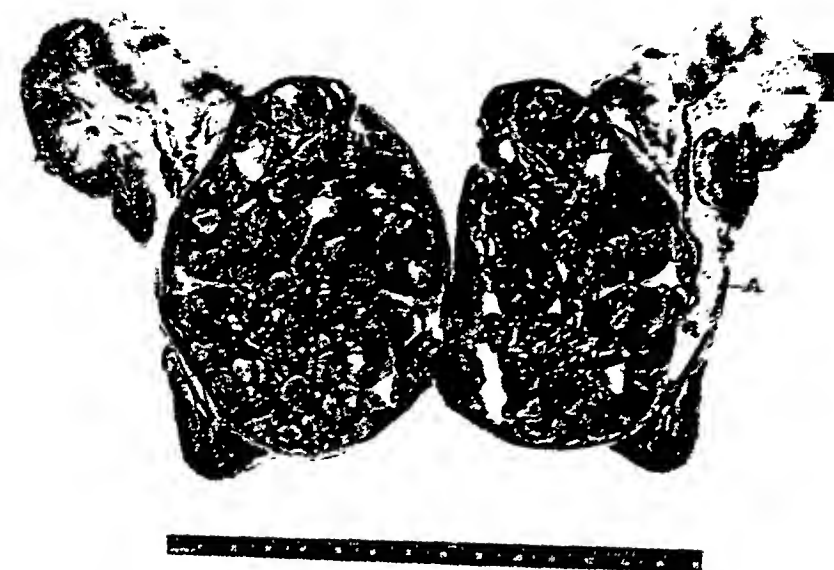


Fig. 2.—Photograph showing the sharp line of demarcation between the kidney and the tumor; A, the dilated renal pelvis. The cystic structure of the tumor is notable.

9 cm. The complete specimen weighed 395 Gm., and measured 14 by 10.5 by 10 cm. The tumor of the lower portion of the kidney was about four fifths of the entire specimen.

On the surfaces made by sectioning, the color of the renal tissue was normal. The cortex was from 6 to 8 mm. thick; it had well defined striations and was clearly in contrast with the medullary portion. The renal substance of the upper pole was from 8 to 15 mm. thick. Here the capsule stripped easily leaving a smooth surface.

From the upper pole the renal tissue thinned on the outer surface to blend with the capsule of the tumor mass. The renal tissue was sharply defined from the tumor by a firm capsule 1 mm. thick (fig. 2). The tissue of the tumor within its capsule had replaced the lower pole of the kidney and had been compressed up and medially into the remaining portion of the kidney.

The tumor tissue, wherever it was cut, consisted uniformly of hundreds of separate cysts with firm, thin, gray walls, which varied in size from 2 to 10 mm. in diameter. The cysts generally contained clear pale brown fluid, but in isolated places, after fixation with a solution of formaldehyde the content appeared as a firm, clear, gelatin-like substance which occasionally, in its center, contained a homogeneous opaque, yellow-brown material. In a few places in which the capsule was not adherent, the cysts occurred in clusters of eight or ten. They extended from the main mass of the tumor, which was firmly compressed within the rigid capsule. The cysts were not present anywhere within the substance of the kidney.

Microscopically the tumor consisted of simple cysts of many sizes. All the cysts were lined with a single layer of flat, broad endothelium and contained lymph (fig. 4). The endothelial cells were more than one layer thick only in isolated places. These places were at the site of a clump of smaller cysts, evidently

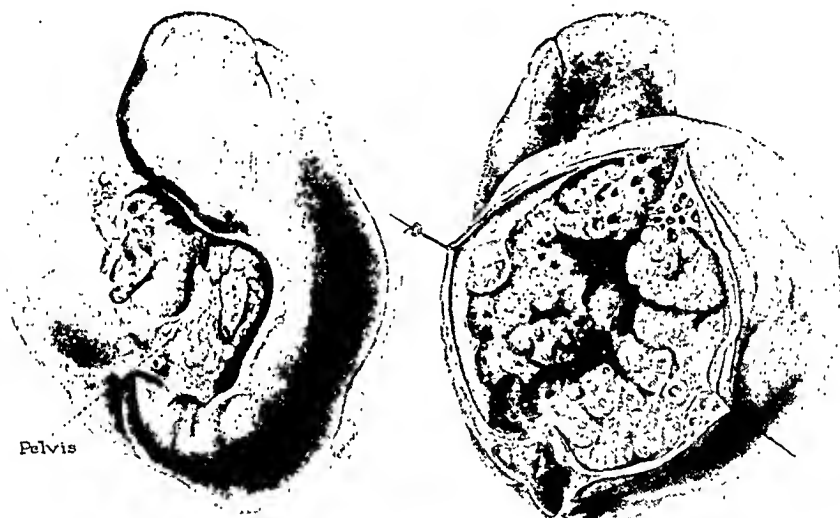


Fig. 3.—The thick capsule of the tumor is made up of hundreds of separate cysts with a firm, thin, gray wall.

at a point of compression by adjacent cysts. The amount of lymph in the compressed cyst was scant, and the hyperplastic endothelium was in the recesses of the cyst and consisted of stratified cuboid endothelium proliferating centrally into the cyst from the cells of the peripheral lining.

The walls of the larger cysts were thin, so that the space between the endothelial lining of the adjacent cysts was a delicate band of fibrous reticular tissue. Elsewhere, however, the endothelial linings of adjacent cysts were separated by dense fibrous reticular tissue in which blood vessels were sparse. In places this fibrous reticulum occupied all of a low power field, and its central portion showed few nuclei, with compression atrophy, degeneration of hyalin and isolated deposition of calcium.

The entire tumor mass, which consisted of lymphatic spaces, was separated from the kidney substance proper by a capsule of dense fibrous tissue (fig. 5). Occasionally the capsule retained isolated renal tubules which were in various stages of atrophy.



Fig. 4.—Photograph showing lymph cysts of variable size typical of the entire tumor.



Fig. 5.—The fibrous wall of the cyst contains solitary cysts with compression of the kidney. Lymphocytic infiltration is evident.

In the kidney, where the tumor had compressed it was a dense infiltration of lymphocytes. The renal substance adjacent to the capsule of the tumor was atrophic, the tubules stained poorly, and many glomeruli were hyalinized. This change of the renal tissue occurred only in that part which was adjacent to the tumor. The tissue of the kidney proper was free from histologic evidence of disease. Cysts were not present anywhere within the substance of the kidney.

#### REVIEW OF THE LITERATURE

The literature on the subject of retroperitoneal lymphangioma is extremely scanty. In the reviews of retroperitoneal tumors by Gobell (1901), Mauclore (1901), Magoun (1919), Andrews (1923) and Schmid (1923), no mention was made of this type of neoplasm. In his review of the literature relative to pararenal tumors Lecène (1919) included 1 lymphangiosarcoma (Lund, 1901) in the series of 113 cases. Gaudier and Gorse (1913) reported a retroperitoneal cystic lymphangioma, and drew attention to the fact that a diligent search of the literature revealed no strictly analogous case. They reviewed, however, the cases of retroperitoneal lymphatic cysts reported by Kilian (1886), Narath (1886), Winter (1895) and Penkert (1902), owing to the fact that these cysts showed some points of similarity to those in their own case.

Westman (1925) reported a retroperitoneal lymphangioma, which was retrocecal. He mentioned no similar case in the literature. Burhaneddin (1931) reported a multilocular cystic retroperitoneal lymphangioma, his comment being that he had not succeeded in finding a similar case in the literature. McFadden (1931) reported a successful removal of a multilocular cystic retroperitoneal lymphangioma by operation.

While there are a number of cases of chylous and lymphatic cysts reported, the 4 cases mentioned constitute the only instances of true retroperitoneal lymphangioma of which we are able to find a record. These, with the addition of the tumor herein reported, furnish 5 such cases for study.

Our survey leads us to concur with the opinion of McFadden who feels that many of the retroperitoneal cysts described in the literature were probably true lymphangiomata and not cysts arising from local peritoneal cells derived from the urogenital ridge. We include in our study, however, only those cases in which the growths were proved by microscopic study to be true neoplasms of the type of lymphangioma. Kaufmann emphasized the necessity of differentiating between lymphangioma, a new growth, and lymphangiectasis, a simple dilatation of the lymphatic vessels.

*Cases of Retroperitoneal Perirenal Lymphangioma Reported in the Literature*

Author	Age, Years	Sex	Duration of Symptoms	Symptoms	Clinical Diagnosis	Method of Diagnosis	Location of Tumor	Size of Tumor, Cu.	Treatment	Outcome	Comment
Gandler and Gorse..... (1913)	1	M	.....	Intrathoracic tumor (diaphragmatic), pressure on right transverse colon, pain in right lateral abdominal wall	Cystic and exfoliating tumor	Operation and examination of specimen	Right retroperitoneal region from lower pole of kidney to pelvis with extension into inguinal region	25 by 10 by 12	Surgical extirpation	Good	Tumor showed a finger-like extension into serotum
Westman..... (1925)	58	M	About 21 years	Tenderness over right side of abdomen, pain in right side of abdomen, nausea and vomiting	Acute appendicitis	Operation and autopsy	Retrocecal, surrounding cecum and appendix	Size of fist	Exploratory operation	Death from gangrenous appendicitis	Tumor prevented removal of appendix, and this caused death
McVadden..... (1931)	5	M	4 years; 4 days	Enlarged abdomen, acute abdominal pain and distention with pushing out of umbilicus	Inflamed appendix or inflamed gland of tuberculous peritonitis	Operation and examination of specimen	Retroperitoneal, extending from lower pole of right kidney to inferior surface of the liver	.....	(1) Drainage of cyst; (2) extirpation of tumor 15 months later	Good	
Thurman..... (1931)	40	M	4 years	Tumor, size of a fist above right inguinal fold, which enlarged to reach right costal arch	Inoperable sarcoma	Operation and histologic study of specimen	Right retroperitoneal region, lying into abdomen and displacing cecum and appendix	45 by 35; weight, 0.4 Kg.	Extirpation by abdominal route (pararectal incision)	Good	
Kretschmer and Hibbs..... (1933)	50	F	8 years; several years	Pain in right upper quadrant of abdomen, mass which almost filled entire right upper quadrant of abdomen	Tumor of right kidney	Operation and histologic study of specimen	Attached to lower pole of kidney	8.5 by 11 by 9	Nephrectomy	Recovery	

## ETIOLOGY

In considering the etiology of retroperitoneal lymphangioma careful distinction must be made between retroperitoneal and mesenteric cysts and true lymphangioma. According to Ewing, retroperitoneal lymphangioma occurs in children and adults as a multilocular cavernous and cystic tumor, originating along the spinal column and ramifying into the pelvis behind the kidney or colon, upward to the liver and the spleen and into the omentum. He stated that "the very early stages and exact origin of these tumors have not been demonstrated," and added that their neoplastic nature seems assured "since the walls contain cellular connective tissue, often much smooth muscle and lymph-follicles."

Magoun's opinion is that the origin of retroperitoneal tumors "is at the best a matter of speculation. All types of tissue are in the retroperitoneal space and may at any moment undergo abnormal growth." Harris said: "The various angiomas must have their origin in a developmental anomaly in structure of certain vascular segments which do not fit into the circulatory system, and which retain embryonal characteristics. The congenital origin of the majority of these tumors speaks strongly in favor of a tissue predisposition as a prominent factor in their genesis."

Burhaneddin mentioned the various types of retroperitoneal cysts and the theories of their etiology, but concluded that his own case was one of cystic lymphangioma—a true neoplasm. McFadden said that while its anatomic relation might have suggested the origin of his case of retroperitoneal tumor (cystic lymphangioma) from the urogenital ridge, examination revealed it to be a true lymphangioma.

The old literature contained references to lymph cysts, according to Westman. Such tumors were regarded as a result of lymph stasis, but at present they are regarded as true new growths.

Brandsburg said that the majority of lymphangiomas occur in childhood, and found that they occur with equal frequency in the two sexes. There are many theories as to their etiology, of which he enumerated four: (1) the retention theory, which explains lymphangioma on the grounds of mechanical pressure; (2) the theory of a disturbance of the secretory function of the endothelium of the vessels, causing hyperproliferation of the lymph, or a disturbance of the permeability of the endothelium; (3) the inflammatory theory; (4) the embryonal theory. Brandsburg believed that the embryonal theory is the most acceptable. It explains the lymphangioma on the grounds of a defect in the embryonal organization of the lymphatic system, small segments of tissue retaining their embryonal characteristics.

## PATHOLOGY

A lymphangioma is a tumor composed of lymph vessels. It is an organoid structure consisting of endothelial cells and supporting connective tissue, both being involved in the neoplastic process.

Ewing stated that the clinical conditions which fall in the general class of lymphangioma "include a variety of slowly growing congenital single or multiple tumors of the skin, subcutaneous tissues, deep areolar structures and muscles of neck, trunk, lip, tongue, eye and orbit." He believed that in the pathogenesis of these conditions many factors are concerned; hence it is more difficult to distinguish between lymphangioma and lymphangiectasis than between true and spurious hemangioma. Ewing thought that the simple occlusion of lymph channels may be followed by extensive varicosities resembling lymphangioma. He noted that the general clinical features apparently offer an important means of recognition of lymphangioma, but even so there are a large number of investigators who would include in the class only such processes as show a congenital origin and a progressive course, with an absence of traumatic and inflammatory factors.

Kaufmann stated that on section a lymphangioma shows dilated spaces lined with endothelium, which are filled with clear or slightly cloudy lymph. The walls are fibrous and often quite muscular. The interstitial tissues contain fat and foci of lymphoid structures, and after section of the tumor the cavities collapse. Collapse of the cavities did not occur in our case. Kaufmann further stated that when the overgrowth of connective tissue is greater between the spaces, the tumor is firmer and may be termed lymphangiofibroma. He contended that in the individual case it is sometimes difficult to determine whether the mass is a true neoplasm of lymphatic vessels or only a dilatation with secondary thickening of preformed vessels with some muscular hypertrophy. A sharp differentiation should be made between lymphangiectasis (simple dilatation of lymph vessels) and lymphangioma (a new growth).

Sick (quoted by Kaufmann) believed that the starting point of many lymphangiomias is in an isolated vessel or primitive connective-tissue rest which proliferates into new lymph vessels.

In Burhaneddin's case (retroperitoneal cystic lymphangioma) the tumor was greenish white, thin walled and made up of cysts of various sizes filled with clear fluid. The tumor had no connection with the tissues around the kidney. On microscopic examination the inner walls of the cysts of Burhaneddin's tumor were seen to be lined with oblong, partly flat endothelial cells. On the external surface and in the interstices between the cysts it was noted that angiomatous tissue was developing. In isolated places the interstitial tissue showed flat, large, cellular



elements, which seemed to fill the spaces of these tissues. The diagnosis, from a study of the structure of these walls, was cystic lymphangioma.

McFadden's case revealed at operation a large cyst shaped like a horseshoe, which filled the lower part of the abdomen. In the midline it reached about an inch (2.5 cm.) above the bifurcation of the aorta, and in the flanks it extended to the pouches of both kidneys. It extended into the pelvis behind the mesosigmoid and mesorectum, was closely adherent to the perinephric fat and was tense and multilocular. In one area colonies of small cysts on the wall of the cyst gave the appearance of frog's spawn. The cysts contained turbid fluid in which were scattered flakes of lymph. Microscopic study showed the tumor to be a true lymphangioma, with a matrix mostly of fatty tissue, though in places it was fibrous with strands of plain muscle among collagen fibrils. In the matrix was a sort of spongy network of channels, some long and narrow, some in the form of wide spaces. The lining of these was a single layer of flattened endothelial cells (absent in some places), which were supported by fibrous tissues. Collections of lymphocytes were seen, sometimes in the walls of the spaces, sometimes lying irregularly in the meshes of the matrix, sometimes in spaces by themselves. Scattered foci of polymorphonuclear leukocytes gave evidence of super-added inflammatory reaction. McFadden noted the similarity of appearance of the cavernous lymphangioma to congenital hygroma of the neck or axilla.

In Westman's case the tumor surrounded the cecum on the anterior, external and posterior sides. It was the size of a clenched fist and was composed of small cysts. The growth was fixed against the posterior abdominal wall, but was easily loosened from the lower pole of the right kidney. It had no union with the appendix, intestines or other organs, and was diagnosed after microscopic study as a lymphangioma cavernosum. There was neither dilatation of lymph vessels nor any evidence of lymphostasis.

Gaudier and Gorse remarked that the pathologic process present in retroperitoneal lymphangioma is obscure. They noted that Penkert discussed the various hypotheses of degeneration of ganglions, dilatation of the lymphatic vessels and cystic degeneration of a cavernous lymphangioma. Other authors were inclined to think that the condition is a congenital malformation. Gaudier and Gorse expressed the opinion that the true explanation is wanting.

The tumor in our case, by its growth, caused pressure atrophy of the lower pole of the kidney and was attached to the kidney.

## SYMPTOMS AND CLINICAL FEATURES

Retroperitoneal lymphangiomas present no clinical features which would serve to distinguish them from other retroperitoneal growths. Retroperitoneal tumors are as a rule "silent" until their size is such that symptoms of pressure arise. Burhaneddin noted that difficult respiration and ureteral pressure are two usual effects of such tumors. In his case (cystic lymphangioma) the neoplasm caused symptoms of ureteral obstruction which were relieved after removal of the mass.

In McFadden's case (retroperitoneal lymphangioma) the patient, who had had an enlarged abdomen for four years, suddenly suffered acute abdominal pain and distention of such degree that there was protrusion of the umbilicus. Palpation did not reveal a tumor, and rectal examination gave negative results. A clinical diagnosis of acute appendicitis or inflamed glands of tuberculous peritonitis was made.

The retroperitoneal lymphangioma reported by Westman had apparently caused no symptoms and was discovered incidentally during an operation for acute appendicitis. The size and position (retrocecal) of the tumor prevented the removal of the gangrenous appendix, thus causing the death of the patient in an indirect manner.

A prolongation of the tumor in the case of retroperitoneal lymphangioma recorded by Gaudier and Gorse caused an inguinoscrotal tumefaction, which served to direct attention to the growth. On examination it was noted that the pressure on the scrotum was transmitted to the right lateral abdominal wall, at which point a large, rounded, painless tumor was palpated. The clinical diagnosis was abdominoscrotal tumor of unknown nature.

In his study of retroperitoneal tumors at the Mayo Clinic, Magoun found the following to be the most prominent symptoms of the group of benign neoplasms:

Abdominal mass.....	15
Loss of weight and strength.....	10
Abdominal pain.....	5
Increase in size of the abdomen.....	2
Pain in the back.....	2
Bloating .....	1
Constipation .....	1
Fulness and belching.....	1
Paresthesia in the right leg by pressure on the growth.....	1

Magoun noted that these symptoms accompanied the group of malignant retroperitoneal tumors; hence he concluded that clinically it was highly improbable that one could distinguish between the types of tumor.

## DIAGNOSIS

The chief aids in the diagnosis of retroperitoneal tumors are cystoscopy, ureteral catheterization and pyelography, since the differential diagnosis of retroperitoneal growths must include a consideration of renal tumor, hypernephroma, hydronephrosis, pyonephrosis and perinephritic abscess. Furthermore, consideration must be given to enlargements of the spleen, both solid and cystic tumors of the pancreas, as well as, in rare instances, to tuberculosis of the lymph nodes.

An old but simple aid in the diagnosis, namely, inflation of the colon with air, has been almost displaced by roentgenography.

When the retroperitoneal tumor occurs low in the abdomen it may be confused with lesions of the uterus or ovaries. Because of the painless nature of the enlargement, retroperitoneal tumors have led to an erroneous diagnosis of pregnancy. It is important to remember that a diagnosis of the nature of the growth, as to whether it is benign or malignant, as well as the differentiation of lymphangioma from other retroperitoneal growths, can be established only by histologic examination of the tumor.

## TREATMENT

At operation for retroperitoneal tumors it is not infrequently necessary to perform a nephrectomy, as in our case, when the kidney is engulfed by the tumor, making removal of the latter without the former a mechanical impossibility. In other instances the kidney has atrophied as a result of the pressure of the neoplasm and is not worth saving, hence the importance of a thorough preoperative study of the function of both kidneys preliminary to operation for retroperitoneal tumor. The knowledge thus gained not only is important from a diagnostic point of view but may be essential during the operation, as nephrectomy may be necessary in the removal of the tumor. Hofstätter and Schnitzler noted that when bands of tissue exist between the kidney and the tumor, it is frequently impossible to tell macroscopically, during the operation, whether the bands are simple adhesions or extensions of the growth. Such a condition would predispose the surgeon to do a nephrectomy, provided he knew that the function of the opposite kidney was satisfactory. Hartmann and Lecène removed the kidney in 18 of 27 cases of pararenal tumor in which they operated.

According to Westman, Lecène, Bettman and Serby, the chief surgical difficulty in the removal of retroperitoneal growths lies in the dissection of the adhesions of the tumor to the mesentery and intestines. These authors note that in such dissection injury to mesenteric vessels may be unavoidable, and may necessitate resection of portions of the intestine. They urge that at operation for retroperitoneal tumors the surgeon and operating instruments be prepared for such an emergency.

It is generally conceded that the ideal treatment of benign retroperitoneal tumors, including the rare cystic lymphangioma, is surgical extirpation. On the other hand, Burhaneddin wrote that it is surprising that the extirpation of such large cystic tumors is frequently possible. Ours was easily removed.

Westman stated that although complete extirpation is the ideal treatment for cystic lymphangioma of the retroperitoneal regions, drainage, with tamponade and suture of the edges of the cyst to the peritoneum, may be done when the tumor is unilocular and when its size and attachments make complete extirpation impossible. He also stated that radium may be used when, for any reason, the tumor cannot be extirpated.

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# PERICARDIECTOMY FOR ADVANCED PICK'S DISEASE

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PHILADELPHIA

Despite an increasing number of reports of cases, particularly from Germany, it remained for the work of Churchill and Beck to awaken interest in this country in the surgical treatment of Pick's disease. In 1929 Churchill<sup>1</sup> in an excellent article on "Decortication of the Heart (Delorme) for Adhesive Pericarditis" reviewed the subject and added a successful case of his own. In 1930 Beck<sup>2</sup> produced Pick's syndrome in dogs by injecting surgical solution of chlorinated soda into the pericardiac cavity. He subsequently obtained a symptomatic cure in these animals by pericardiectomy. Beck also reported a successful pericardiectomy on a human being.

The pathologic physiology of concretio pericardii, or callous pericarditis, commonly known as Pick's disease, need not be discussed at length, as it has already been admirably described by Rehn,<sup>3</sup> Volhard and Schmieden,<sup>4</sup> Churchill,<sup>1</sup> Beck<sup>2</sup> and others. The essential pathologic change is a marked fibrous thickening of the pericardium which limits the normal diastolic expansion of the heart. Extrapericardiac and intrapericardiac adhesions are not an essential feature of the condition, although the latter are almost invariably present. The symptoms arise chiefly from the marked venous stasis and resemble those of chronic congestive cardiac failure. The diagnostic features are illustrated in the case reported here. The only treatment for this obvious mechanical impediment to the circulation<sup>5</sup> is the removal of the pericardium.

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In the following case advanced Pick's disease was unsuccessfully treated by pericardiectomy. The failure is attributed to the presence of a thickened epicardium which was not removed at operation.

#### REPORT OF A CASE

*History.*—The patient was an Italian boy, aged 12. When he was 3 years old a mass had appeared on one side of his neck. This was incised, and a small amount of pus evacuated. The following year his parents noticed that he was not as large or as strong as his brothers and sister. In the summer of 1928, when 7 years old, he became easily fatigued on slight exertion, and his abdomen slowly increased in size. He was treated for cardiac disease by the family physician. The swelling persisted until the weather became cold, when it subsided completely. Tonsillectomy was performed at that time.

In the summer of 1929 the abdomen again became enlarged, but the swelling disappeared in the winter. In June, 1930, the swelling reappeared, and about 3,500 cc. of cloudy fluid was aspirated from the abdomen. Digitalis was given in varying amounts that summer without noticeable effect on the ascites. There was a slight puffiness under the eyes in the morning, and dyspnea on exertion when the abdomen was enlarged. Later in the summer the legs and scrotum became edematous, but following a second paracentesis of 4,000 cc. the edema disappeared.

The patient was first admitted to the Pennsylvania Hospital in November, 1930. He was then 10 years of age. He appeared undernourished, his arms and legs were thin, and his abdomen was enormously enlarged. There was no dyspnea, cyanosis or dependent edema. The veins of the neck, arms and abdomen were prominent. There was no clubbing of the fingers. The right border of the heart was 1.5 cm. from the midline in the right third interspace, and the left border 7 cm. from the midline in the left fifth interspace. The cardiac impulse was diffusely visible and palpable. There were no murmurs, and the heart sounds were of good quality. Marked ascites and a moderate-sized umbilical hernia were present. The blood pressure was 98 systolic and 72 diastolic. Four thousand cubic centimeters of clear yellow fluid, with a specific gravity of 1.018, was removed by abdominal paracentesis. No tubercle bacilli were found on smear or culture of the fluid. The liver was enlarged but not tender. The Wassermann reaction of the blood was negative, and the urine was normal, the specific gravity varying between 1.015 and 1.030. The total serum protein was 3.03 per cent; the albumin, 2.14, the globulin, 0.89, and the albumin-globulin ratio, 2.4. A roentgenogram of the chest showed an angular projection from the left side of the cardiac shadow, presumably due to an extrapericardiac adhesion. The right cardiac border was smooth. The transverse diameter of the heart was 101 mm., that of the chest, 197 mm. The patient's temperature varied between 97 and 100 F. and the pulse rate between 92 and 108. A diagnosis of cirrhosis of the liver was made. A salt-free diet was given, but the ascites recurred rapidly, and paracentesis was again necessary before his discharge from the hospital in December.

His abdomen did not require tapping again until June, 1931, when the patient was admitted to the Jefferson Hospital. Paracentesis was performed every three or four weeks in the hospital, and the fluid assumed a milky character. A guinea-pig was inoculated with the ascitic fluid, and special cultures for the tubercle bacillus were made, but no evidence of tuberculosis was found. The total protein content of the ascitic fluid varied between 3.36 and 2.19 per cent. In August, 1931, an exploratory laparotomy was performed by another surgeon. He found a smooth,

markedly thickened peritoneum, but no evidence of tuberculosis. The liver was slightly enlarged with rounded edges and had a thick white coating dotted with shallow depressions somewhat resembling the icing on a cake. The spleen was about three times the normal size, and its surface resembled that of the liver. A specimen of hepatic tissue was removed for microscopic study. It showed marked thickening of the capsule and dilatation of the sinusoids about the central efferent veins, with early necrosis of hepatic cells in that area. The lesion was similar to that observed in chronic passive congestion. There was a slight irregular fever during the patient's stay in the hospital. He was discharged in October, 1931. From that time until June, 1932, his abdomen was tapped every four weeks. Edema of the lower extremities and scrotum appeared in January, 1932, and gradually increased.



Fig. 1.—Appearance of the patient before operation. In the profile view the prominence and distention of the external jugular vein in the erect posture can be seen.

On his second admission to the Pennsylvania Hospital, June, 1932, his abdomen was enormously distended with fluid, and there were large scrotal and umbilical hernias. The legs and scrotum were edematous. The veins of the forearms, hands, feet, neck and chest were very prominent. The hands and feet were cold and cyanotic. There were moist, coarse râles at the bases of the lungs. Five thousand and five hundred cubic centimeters of fluid, containing 4 per cent protein, was removed from the abdomen. Following paracentesis the râles in the lungs disappeared. He remained in the hospital a few days and was then treated in the outpatient department. Abdominal paracentesis was necessary every two or three weeks during the summer.

He was readmitted on Oct. 14, 1932, for the purpose of confirming the diagnosis of Pick's disease, which had been suggested. The veins of the hands were unusually prominent. The external jugular veins were pulsating and distended, even in the erect posture (fig. 1). There was a definite pulsus paradoxicus. The

blood pressure was 78 systolic and 66 diastolic. The anteroposterior diameter of the chest was increased so that it assumed the barrel shape of chronic emphysema. The percussion note was resonant over the lungs. Breath sounds were vesicular and no râles were heard. Hepatic dulness began at the fifth rib in the right midclavicular line anteriorly. The lower border of the liver was easily palpable two fingerbreadths below the costal margin. The edge was rounded, and the surface smooth, firm and not tender.

There was no bulging of the precordium or visible cardiac impulse. The apex beat was not palpable. The area of cardiac dulness was slightly larger than



Fig. 2.—Roentgenograms of the chest, taken at a distance of 6 feet, before and after pericardiectomy: *A*, Oct. 17, 1932; *B*, Dec. 12, 1932. There is a slight increase in the cardiac area after operation.

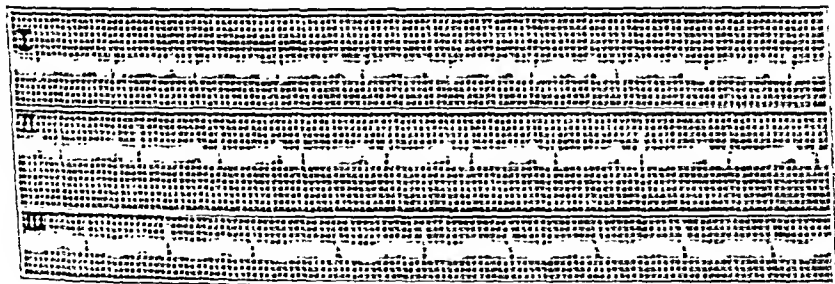


Fig. 3.—Electrocardiogram, taken on Nov. 3, 1932. No axis deviation is apparent. The QRS complexes are slurred and of very low amplitude in all the leads. The T waves are of low amplitude in lead I, iso-electric in lead II and inverted in lead III. The resistance was 1,700 ohms.

normal. The right border was 2.5 cm. from the midline in the third interspace, and the left border, 7.5 cm. in the fifth interspace. The cardiac sounds were clear, with the exception of a slight prolongation of the first sound at the apex. There was soft pitting edema of the legs below the knees.

No cardiac pulsation could be seen on fluoroscopic examination. The cardiac outline on the roentgenogram was irregular (fig. 2*A*). The transverse diameter of the heart was 120 mm.; that of the chest, 211 mm., representing an increase of 19 mm. in the heart and 14 mm. in the chest since November, 1930. An electrocardiogram (fig. 3) showed the very low voltage, the flat T waves, and the slur-



ring of the Q R S complex which were present in Beck's patient.<sup>2</sup> During October and November the venous pressure in the left median basilic vein varied between 24.5 and 22.5 cm. of water. There was no significant change in the venous pressure after paracentesis, which was performed every two or three weeks. As the history and results of the examination all indicated a far advanced and progressive case of Pick's disease, it was thought that pericardiectomy offered the only hope for improvement.

*Pericardiectomy.*—The operation was performed on Nov. 21, 1932. The patient was placed on the operating table with the head and chest elevated about 20 degrees. Under ether anesthesia a curved incision was made from the second left costochondral junction to the midsternal line, then down and laterally over the seventh costal cartilage. The flap of skin and of pectoralis major muscle was reflected outward. The third, fourth, fifth, sixth and seventh costal cartilages were excised. A portion of the left side of the sternum from the third to the sixth rib was removed with rongeur forceps. The posterior layer of the perichondrium of the cartilages and the exposed intercostal muscles were excised. This exposed the left internal mammary vessels, the anterior border of the left pleura and a small portion of the anterior surface of the pericardium. The pleura and the internal mammary vessels were retracted to the left and separated from the pericardium by blunt dissection. The right lung and pleura were similarly treated. At one time it was thought that the right pleural cavity had been opened, because of a "swishing" sound synchronous with respiration. The suspected area was covered with rubber dam and later with petrolatum gauze. On removal of these, at the close of the operation, no opening in the pleura was evident.

The exposed pericardium was light gray. Calcareous deposits were palpable in and beneath the pericardium, especially in the region of the right auricle. The pericardium was incised longitudinally from the pulmonary artery to the diaphragm. The heart bulged slightly through the incision. The pericardium was adherent to the epicardium throughout. It was separated from the heart by blunt dissection with the finger. In only one place, over the wall of the right ventricle, was it necessary to employ scissors to divide a calcareous band, 4 or 5 mm. thick, between the heart and the pericardium. The surface of the exposed heart was dull gray. Small, thin, calcareous plaques could be seen and felt in the thickened epicardium. These were especially numerous at the base, over the auricles and the great vessels. On palpation the sensation was that of passing the finger over coarse sandpaper. The pleural reflections were now further separated from the external surface of the pericardium. The separation was facilitated by making lateral traction on the edges of the pericardium, thus rotating the heart first to the right and then to the left. This maneuver was particularly useful in separating the right pleura from the pericardium. The anterior surface of the pericardium was then resected (fig. 4), the left side being removed first. The apex of the heart was elevated and the heart freed posteriorly. A narrow V-shaped strip was removed from the thickened diaphragmatic pericardium. There were no bands constricting the inferior vena cava.

The flap of skin and muscle was replaced over the defect in the thoracic cage, thus bringing a small portion of the right ventricle in direct contact with the under surface of the pectoralis major muscle. The wound was approximated in layers and closed without drainage. A gauze pad was firmly strapped over the wound with adhesive plaster to control the paradoxical movement of the chest wall.

The veins in the neck were still prominent at the conclusion of the operation with the patient in the semirecumbent position. The blood pressure the day before the operation was 78 systolic and 66 diastolic. Before the administration of the anesthetic on the day of the operation, it was 96 systolic and 78 diastolic; the day after the operation it was 88 systolic and 54 diastolic. The increase in the pulse pressure was maintained on subsequent readings until the patient was discharged.

There was little postoperative reaction. On the seventh day, several ounces of clear serum drained from the lower portion of the wound, spurting with the



Fig. 4.—The portions of the pericardium and the costal cartilages excised at operation.

heart beat. This drainage continued for a few days and then ceased. A superficial infection of the upper portion of the wound also occurred but subsided promptly. For three weeks after the operation there was a slight reduction in the rapidity with which the ascitic fluid accumulated. Thereafter little difference could be observed. The venous pressure was 17 cm. of water nine days after the operation, but rose to 25 cm. of water, slightly above the preoperative level, on the twentieth day. It was still impossible to observe any cardiac or aortic pulsation by fluoroscopy. There was an increase of about 4 mm. in the transverse diameter of the heart after the operation (fig. 2 B). A postoperative electrocardiogram was essentially similar to the one taken before the operation.

The patient left the hospital on December 18, twenty-seven days after the operation. He returned on December 27 for abdominal paracentesis and was discharged the following day. The wound in the chest had healed. The veins in the neck were still prominent, the abdomen was distended, and there was pitting edema of the legs below the knees. Five thousand and five hundred cubic centimeters of fluid was removed from the abdomen.

On Jan. 6, 1933, the patient was readmitted, with marked dyspnea and cyanosis. The abdomen was distended and there was edema of both lower extremities. The

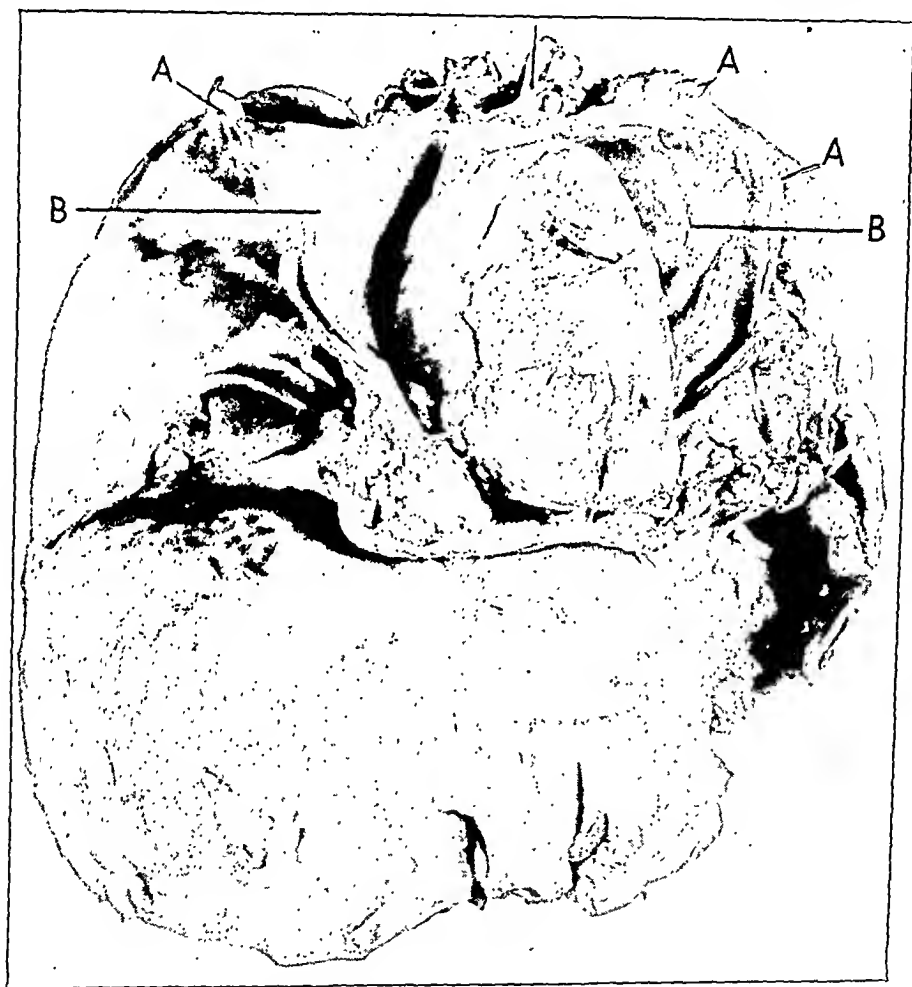


Fig. 5.—The heart, lungs and liver removed en masse at autopsy. At *A*, traction is made on the thickened pleural reflections overlying the heart. The remaining portion of the pericardium has been separated from the heart, and the line of operative resection may be seen at *BB*. The pectoralis major muscle and short segments of three costal cartilages can be seen adhering to the anterior surface of the heart. The heavy irregular deposit of fibrin dotted with shallow depressions is evident on the surface of the liver.

pulse rate was about 160 per minute and the blood pressure was 70 systolic and 50 diastolic. Shortly after admission 5,700 cc. of fluid was removed from the abdomen. Pulmonary edema developed four or five hours later, and despite stimulation and inhalation of oxygen, the patient died.

*Autopsy.*—Autopsy was performed eight hours after death. On opening the peritoneal cavity 2 liters of clear amber-colored fluid was removed. The peritoneum was 1.5 mm. thick, but its surface was smooth and glistening. The omentum was small and adherent to the anterior parietal peritoneum in the left upper quadrant of the abdomen. Both lobes of the liver were enlarged, extending two or three fingerbreadths below the costal margin. The entire anterolateral surface of the liver was densely adherent to the diaphragm and the parietal peritoneum. The surface of the liver was covered with a thick white mottled coating (fig. 5). The spleen was not adherent, and its capsule was similar in appearance to that of the liver. The other abdominal organs were grossly normal.

The pleural cavities were entirely obliterated by adhesions. Both pleurae were densely adherent to the pericardium. The pectoralis major muscle was firmly attached to the anterior surface of the heart where the pericardium had been



Fig. 6.—Section of the heart through the left ventricle. The epicardium has been pulled up to illustrate the plane of cleavage between it and the layer of fat lying directly on the myocardium.

removed at operation (fig. 5). The remaining portion of the parietal pericardium was again adherent to the heart, although it had been completely separated at operation. The adhesions could be separated everywhere by blunt dissection with the finger except for a dense band at the apex of the left ventricle, which had to be cut. No obstruction of the inferior and superior vena cava could be demonstrated. Even before the separation of the pericardium from the heart, the finger could be passed through the inferior vena cava into the right auricle and into the superior vena cava without meeting any obstruction or kink. The epicardium was thickened and calcified, as noted at operation. In one place the calcification extended through the left ventricular muscle to within 1 mm. of the endocardial surface. It was found that the epicardium could be stripped with comparative ease from the surface of the ventricle of the heart, from which it was generally separated by a layer of fat (fig. 6), except in places where the calcification pene-

trated through the epicardium into the cardiac muscle. The coronary vessels lay for the most part within the subepicardial fat and the myocardium and were not injured in separating the epicardium from the cardiac muscle. The borders of the mitral valves were slightly thickened and nodular at the attachment of the chordae tendineae. The width of the largest of these nodules was 3 mm. The other cardiac valves were entirely normal. The aorta was smooth and elastic, and the coronary vessels and orifices were patent and not diseased. After removal of the remaining pericardium the heart weighed 150 Gm., which is about normal for a child of this age.<sup>6</sup>

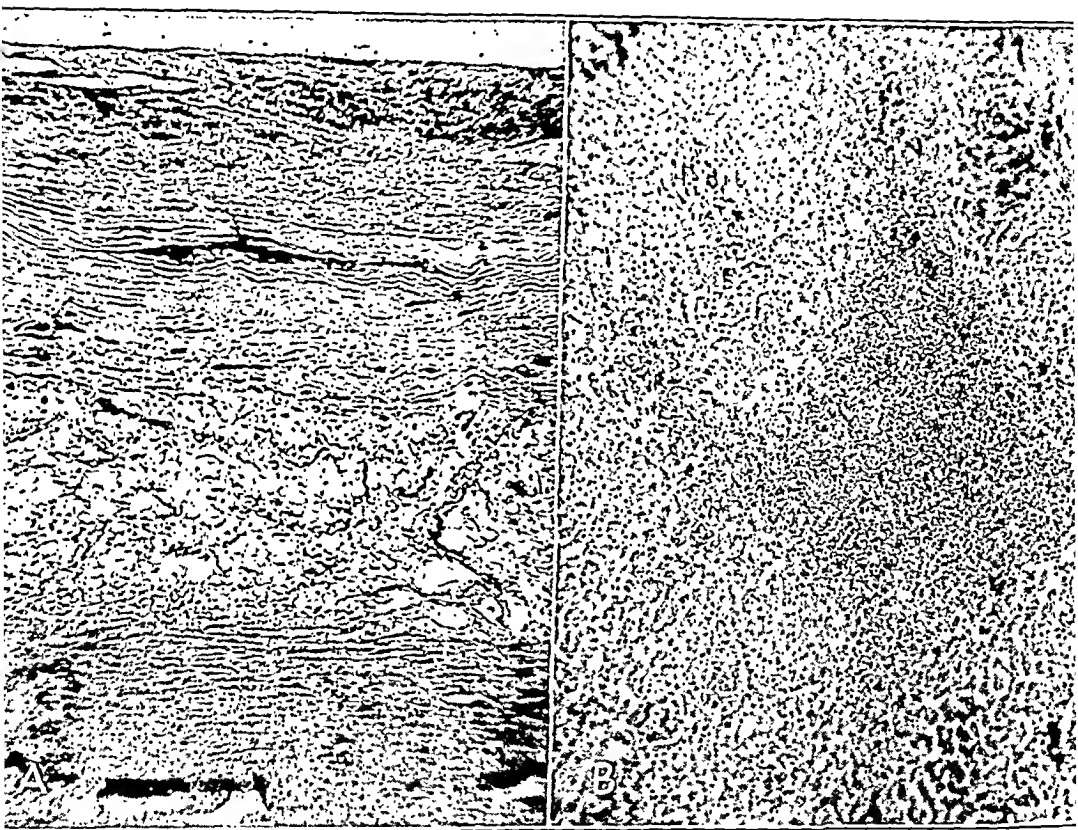


Fig. 7.—*A*, cross-section of epicardium and myocardium;  $\times 43$ . *X*, thickened epicardium; *Y*, layer of fatty tissue and *Z*, external portion of myocardium. *B*, section of hepatic tissue ( $\times 60$ ), showing dilated sinusoids and necrosis of hepatic cells particularly about the efferent veins. The hepatic cells about the portal systems show the least evidence of damage.

A photomicrograph of a section of tissue from the right ventricle is shown in figure 7*A*. Sections of the liver (fig. 7*B*) and spleen showed the changes associated with a severe grade of chronic passive congestion. There was no evidence of tuberculosis in the lungs.

#### COMMENT

In this case the diagnosis of a thickened, constricting pericardium should have been made much earlier. In a child the history of recurring and persistent formation of ascitic fluid and dependent edema, in the

absence of obvious cardiac disease or of impairment of renal function, is highly suggestive. The low pulse pressure and high venous pressure in the absence of valvular lesions of the heart are significant findings. The electrocardiogram was similar to the one reported by Beck.<sup>2</sup> The complete absence of any visible pulsation of the heart under the fluoroscope is a striking and significant sign. The absence of either visible or palpable pulsation over the precordium in conjunction with the other physical findings points to a markedly thickened pericardium. The cardiac area as determined by the orthodiagram was slightly larger than normal for a child of that age, height and weight. The cardiothoracic ratio in a roentgenogram of the chest taken at a distance of 6 feet (183 cm.) was 0.57, which is at the upper limit of normal.<sup>6</sup> Congestive failure in the presence of a small or normal-sized heart has been mentioned as a diagnostic point in Pick's disease.<sup>4</sup> However, the means at our disposal for determining cardiac area during life do not distinguish between the heart itself and its enveloping membranes. A markedly thickened pericardium and pleura will slightly increase the cardiac area, and thus in advanced Pick's disease the cardiac area may be larger than normal, although the heart itself is of normal size. A shift in the electrical axis with a change from the right to the left lateral recumbent position occurred in this patient. Fixation of the electrical axis with change in the position of the body is therefore an inconstant finding in Pick's disease.

Little additional information on the etiology of the disease is afforded by this case. From the study of a large number of autopsies, Sprague, Burch and White<sup>7</sup> conclude that the condition is probably not rheumatic but results from a tuberculous pericarditis. No evidence of tuberculosis was found at autopsy in this patient. The cervical mass which was incised and drained in childhood may or may not have been tuberculous. No member of the patient's immediate family had tuberculosis. On the other hand, there was no history of rheumatic fever, arthritis or chorea. No Aschoff bodies were found in the myocardium. The edges of the mitral valves were slightly but definitely thickened. The other cardiac valves were entirely normal. As Beck has produced the typical Pick's syndrome by chemical irritation of the pericardium, it is probable that any infection of the pericardium of sufficient severity may result in the disease.

The failure to obtain a cure or marked improvement in this patient after removal of the anterior portion of the pericardium may be ascribed

6. White, P. D.: *Heart Disease*, New York, The Macmillan Company, 1931.

7. Sprague, H. B.; Burch, H. A., and White, P. D.: *Adherent Pericardium and Pick's Syndrome: An Autopsy Study*, *New England J. Med.* 207:483 (Sept. 15) 1932.

to the presence of a thickened, calcified epicardium. It was thought that the patient's condition after removal of the pericardium did not justify prolonging the operation in order to remove the epicardium. It was planned, if necessary, to expose the heart again at some later date and to remove as much of the epicardium as possible. The feasibility of stripping this membrane from the surface of the ventricles was demonstrated at autopsy. A layer of subepicardial fat separated the thickened epicardium from the coronary vessels and the myocardium (figs. 6 and 7 *A*), so that the epicardium could be separated by blunt dissection, without injuring either the coronary vessels or the cardiac muscle. In one or two places where calcification extended from the epicardium directly into the myocardium, the separation would have been impossible.

The condition of the epicardium and the clinical course of this patient were closely similar to those described by Beck<sup>2</sup> in experiment 8 (dog 29-31). Pick's syndrome was produced in this dog by the injection of surgical solution of chlorinated soda into the pericardiac cavity. Resection of the parietal pericardium in two stages resulted in a temporary improvement. The syndrome recurred, however, and the dog died. At autopsy the heart was found encased in a tough, thickened epicardium which, as Beck pointed out, undoubtedly interfered with the normal diastolic filling of the heart, as had the thickened pericardium which had been removed at operation. Beck suggested that such a condition might occur in patients and might necessitate the removal of a portion of the epicardium. It is apparent that in some cases of Pick's disease removal of the pericardium alone is sufficient to produce a dramatic alleviation of symptoms.<sup>8</sup> In the far advanced cases, with a thickened and constricting epicardium, resection of a portion of the epicardium is probably necessary. Schmieden<sup>9</sup> even regarded resection of the epicardium as the essential feature of the operation.

The low values for serum protein observed in this patient two years before operation were subsequently overlooked, and unfortunately the determination was not repeated. The total serum protein, 3.03 per cent, and the serum albumin, 2.14 per cent, were both below the usual level at which edema appears.<sup>10</sup> The reason for the low serum proteins in this case is not clear. There was no albuminuria, and the patient's diet contained an adequate amount of protein. On four occasions the protein content of the ascitic fluid lay between 4.0 and 2.19 Gm. per hundred cubic centimeters. Assuming the protein content of the ascitic

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8. Churchill.<sup>1</sup> Beck.<sup>2</sup>

9. Schmieden, V.: *The Technique of Cardiolytic Surgery*, Gynec. & Obst. **43**:89 (July) 1926.

10. Moore, N. S., and Van Slyke, D. D.: *The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis*, J. Clin. Investigation **8**:337 (April) 1930.

fluid to be 2 per cent, the patient lost approximately 7 Gm. of protein per day by paracentesis in the five weeks prior to the operation. This is comparable to the albuminuria in certain cases of nephritis with edema.<sup>11</sup> However, the low serum proteins found two years before the operation could not be explained on this basis, because comparatively small amounts of ascitic fluid were being lost at that time. The reduction in the serum protein content which frequently occurs in cardiac decompensation suggests the possibility that the long-standing hepatic congestion with its attendant injury to hepatic parenchyma may be responsible for the condition. There is, however, no evidence that either serum albumin or globulin is influenced by hepatic injury.<sup>12</sup> Indeed, Payne and Peters<sup>13</sup> have recently observed that the low serum albumin frequently found in cardiac failure appeared "to be directly referable to malnutrition." As our patient was definitely undernourished, the same explanation may apply. The importance of determining the serum proteins in patients with Pick's disease is obvious. If the protein content is low a second factor is brought into play in the production of the edema and ascites which may well be as potent as the increased venous pressure.

#### SUMMARY

An anterior partial pericardiectomy was performed on a 12 year old boy with advanced Pick's disease. The thickened calcified epicardium was not removed. There was slight temporary improvement after the operation, but death occurred forty-six days later. At autopsy adhesions were found to have reformed between the heart and the remaining portion of the pericardium. The failure to relieve the patient of his symptoms was attributed to the presence of a thickened epicardium. The significance of the low serum proteins found prior to operation has been discussed.

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11. Linder, G. C.; Lunsgaard, C., and Van Slyke, D. D.: The Concentration of Plasma Proteins in Nephritis, *J. Exper. Med.* **39**:887 (June) 1924.

12. Peters, J. P.; Eisenman, A. J., and Bulger, H. A.: The Plasma Proteins in Relation to Blood Hydration: I. In Normal Individuals and in Miscellaneous Conditions, *J. Clin. Investigation* **1**:435 (June) 1925.

13. Payne, S. A., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration; Serum Proteins in Heart Disease, *J. Clin. Investigation* **11**:103 (Jan.) 1932.



# TREATMENT OF MYOSITIS, ARTHRITIS AND DISTURBANCES OF THE PERIPHERAL CIRCULATION WITH HISTAMINE BY CATAPHORESIS

DAVID H. KLING, M.D.

LOS ANGELES

Recent investigations have emphasized the significance of disturbances of the peripheral circulation in the etiology of conditions of the joints and muscles. In 1909, Wollenberg,<sup>1</sup> on the basis of arteriosclerotic changes in the affected joints, advanced the theory of the vascular origin of osteo-arthritis; he experimentally produced overgrowth of the patella by a circular ligation of the blood vessels. The experiment was recently repeated and confirmed by Goldhaft<sup>2</sup> and his co-workers, who had previously demonstrated, in studies of the blood flow, blood gases, capillary microscopy and surface temperature, a deficiency of peripheral circulation in arthritis. Hench, Henderson, Rowntree and Adson,<sup>3</sup> of the Mayo Clinic, reported good results in rheumatoid arthritis with ramisection and sympathetic ganglionectomy, which eliminated the vasoconstriction. Von Papp<sup>4</sup> stated that a spasm of the arterioles produces myalgia. The beneficial effect of physical therapy in rheumatic infections is also considered to be due chiefly to a temporary increase of blood supply.

On the basis of extensive studies, Lewis<sup>5</sup> considered histamine-like substances to be the hormone regulating the peripheral circulation. Deutsch<sup>6</sup> therefore conceived the idea of supplying the affected parts with histamine and thus overcoming a possible deficiency. In 1931 he reported favorable results with treatment by galvanic cataphoresis of

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From the Arthritis Department of the Cedars of Lebanon Hospital, Los Angeles.

Read before the Society of Physical Therapy, New York, Feb. 1, 1933.

1. Wollenberg, G. A.: *Aetiologie der Arthritis in Lichte des Experiments*, Arch. f. orthop. u. Unfall-Chir. **7**:226, 1908-1909.

2. Goldhaft, A. D.; Wright, L. M., and Pemberton, R.: *The Production of Hypertrophic Arthritis by Interference with the Blood Supply*, Am. J. M. Sc. **180**:386 (Sept.) 1930.

3. Hench, P. S.; Henderson, M. S.; Rowntree, L. G., and Adson, A.: *Treatment of Chronic "Infectious" Arthritis by Sympathetic Ganglionectomy and Sympathetic Trunk Resection*, J. Lab. & Clin. Med. **15**:1247 (Sept.) 1930.

4. von Papp, quoted by Bettmann.<sup>13</sup>

5. Lewis, T.: *The Blood Vessels of the Human Skin and Their Response*, London, Shaw & Sons, Ltd., 1917.

6. Deutsch, Dezso: *Histamin zur Therapie rheumatischer Erkrankungen*, Med. Klin. **27**:1491 (Oct. 9) 1931.

histamine in 250 cases of painful conditions of the muscles. His findings were confirmed by a number of German investigators (Kopits,<sup>7</sup> Trumpp,<sup>8</sup> Friedländer,<sup>9</sup> Payer,<sup>10</sup> Rosenblüth-Ronald,<sup>11</sup> Vas,<sup>12</sup> and Bettmann<sup>13</sup>). Failure with this method was reported only by Ruhmann<sup>14</sup> and Kauffmann.<sup>15</sup>

Through the support of Dr. Jerome Weiss, I was enabled to introduce this method in the Hospital for Joint Diseases.

#### PHARMACOLOGY OF HISTAMINE

Histamine is, according to Sollmann,<sup>16</sup> a product of the cleavage of proteins by acid, ferments or bacteria. It is found in all tissue extracts and is present in large amounts in the normal stool. But it in turn is rapidly destroyed by bacteria and is therefore not effective when given by mouth. Subcutaneous or intravenous injections of histamine have powerful effects on the circulation and smooth muscles. It is partly responsible for the ergot-like effect on the uterus: it constricts bronchioles and the larger arteries and dilates the arterioles and capillaries. Injections of quantities of more than 1 mg. may therefore cause alarming symptoms, consisting of headache, vomiting, a fall in blood pressure and respiratory disturbances. The theory was advanced that posttraumatic shock is due to liberation of histamine by the damaged tissues.

7. Kopits, I.: Beiträge zur Definition, Differentialdiagnostik und Therapie "rheumatischer Erkrankungen." Arch. f. orthop. u. Unfall-Chir. **31**:7, 1932.

8. Trumpp, Rolf: Neue Behandlung der Muskelschmerzen. München. med. Wchnschr. **78**:1862 (Oct. 30) 1931.

9. Friedländer, quoted by Deutsch, D.: Zur Behandlung von Schmerzen mit Histamin [Comment on Kauffmann's article]. Deutsche med. Wchnschr. **58**:827 (May 20) 1932.

10. Payer, A., quoted by Deutsch.<sup>9</sup>

11. Rosenblüth-Ronald, E.: Die Histamin-Iontophorese und ihre therapeutische Bedeutung. Med. Klin. **28**:1561 (Nov. 4) 1932.

12. Vas, Stefan: Erfahrungen mit der kataphoretischen Histaminbehandlung. Deutsche med. Wchnschr. **58**:1009 (June 24) 1932.

13. Bettmann, Ernst: Neue Wege der Histaminbehandlung schmerzhafter Muskel-, Nerven- und Gelenkerkrankungen, Deutsche med. Wchnschr. **58**:1008, 1932.

14. Ruhmann, Walter: Die örtliche Histamin-Einwirkung bei Muskelrheuma. München. med. Wchnschr. **78**:2201 (Dec. 25) 1931.

15. Kauffmann, M.: Histamine in der Behandlung von Schmerzen, Deutsche med. Wchnschr. **58**:660, 1932.

16. Sollmann, Torald: A Manual of Pharmacology. Philadelphia, W. B. Saunders Company, 1932.

## INFLUENCE OF HISTAMINE ON THE PERIPHERAL CIRCULATION

A simple experiment demonstrates the powerful influence of histamine on the peripheral circulation. One drop of a 1:1,000 solution of histamine is placed on the skin, which is subsequently pricked by a sharp needle. Within five minutes an urticarial wheal surrounded by a red flare will develop (fig. 1). The response of the peripheral circulation consists of a triple reaction: (1) a local dilatation and an increase in the blood flow in the minute vessels (purple spot); (2) a local increase in the permeability of the capillaries, which produces the wheal, and (3) a widespread dilatation of the surrounding arterioles (flare).

This reaction<sup>17</sup> was used by Jordan for the diagnosis of the degree and severity of disturbances of the peripheral circulation in Buerger's disease and arteriosclerosis.

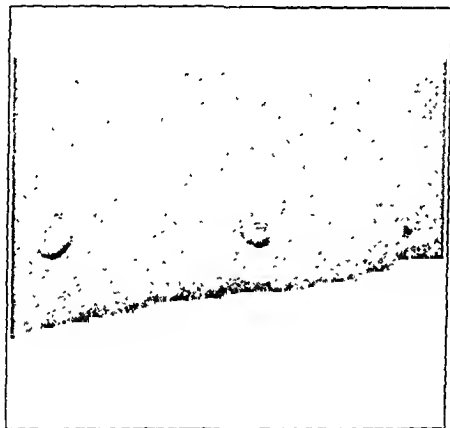


Fig. 1.—Stages in the cutaneous reaction of histamine, showing the flare and the wheal.

## TECHNIC OF APPLYING HISTAMINE

*Cataphoresis.*—Deutsch devised for the purpose of cataphoresis a battery galvanic apparatus; he used leaf impregnated with histamine in conjunction with it. The following technic was therefore adopted: A galvanic apparatus equipped with an accurate milliammeter supplies the electric energy. For electrodes, lead foil is used. Blotting paper is moistened with a 1:1,000 aqueous solution of histamine acid phosphate and applied to the affected part. The positive electrode is adjusted over the blotting paper and secured with rubber bandages. Because of the danger of producing burns, care must be taken that the electrode does not touch the bare skin, and all metal should be removed from the vicinity of the current. A convenient negative electrode consists of a nonmetal basin filled with a weak physiologic solution of sodium chloride in which lead foil connected with the negative pole is placed at the bottom of the basin and covered with a rubber sheet. The hand is immersed in the solution. The current is slowly built up to from

17. Starr, I., Jr.: Change in Reaction of Skin to Histamine as Evidence of Deficient Circulation in Lower Extremities, *J. A. M. A.* 90:209 (June 30) 1928.

4 to 10 millamperes, about from 1 to 2 millamperes to the square inch of positive electrode being allowed. The current is permitted to act for from one to two minutes.

In the majority of cases no more than a sensation of prickling is felt over the treated part. The current is gradually decreased; contact should not be interrupted suddenly.

By serial connection, with branching cords to the positive pole, a number of parts can be treated simultaneously.

*Modification of the Histamine Treatment by Cataphoresis.*—An article on this method was recently published by Bettmann.

A nonmetallic (glass, enamel) basin is filled with a 1:10,000 solution of histamine and connected with the positive electrode: it is insulated by a cover of rubber sheeting. The affected extremity is submersed in the histamine. The negative electrode is wrapped in insulating material (linen, towles or rubber) and applied as a cuff over the part to be treated. The current is permitted to act for from five to ten minutes. This method is most convenient in infections of the hands and feet. Drawbacks are the large amounts of fluid necessary and the frequent renewal, as the weak solution deteriorates in from one to three days. The reaction also is not so strong as with the former method.

*Scratch Method.*—In cases in which a galvanic apparatus was not at hand I have used the following method of application of histamine: The skin is cleansed with gasoline; with a sharp-pointed instrument scratches of about  $\frac{1}{4}$  inch (0.63 cm.) in length are drawn over the affected area in vertical and horizontal directions. The entire area is thus divided into small squares. A piece of gauze is saturated with the 1:1,000 solution of histamine and rubbed into the scratches.

#### EFFECTS OF THE APPLICATION OF HISTAMINE

I studied the changes taking place in patients and in myself after the application of histamine by these methods.

The exposed skin appeared reddened immediately after the removal of the positive electrode. Soon wheals cropped up (fig. 2) and blended into one patch of urticaria (if cataphoresis was used) or into stripes of urticaria (if the scratch method was used). The temperature over the treated parts rose from 2 to 3 degrees C. (3.6 to 5.4 F.). Gradually the elevation of the skin receded, leaving red spots. The skin returned to its normal appearance in from five to six hours.

Bettmann studied the capillary changes and found a marked increase in the rate of circulation and the number of capillaries visualized and dilatation of the subpapillary vessels. He demonstrated experimentally the marked influence of cataphoresis of a 10 per cent solution of sodium iodide preceded by an application of histamine on the resorption of the skin of rabbits. Controls treated only with iodine by cataphoresis showed, in the section, particles of iodine precipitated with thallium acetate in the superficial layers of the corium, while the sections of the skin which were subject to preceding histamine cataphoresis showed

iodine particles scattered through all the layers. Bettmann claimed also that after prolonged treatment the effect on the capillaries can be demonstrated to last for weeks.

Another evidence of the effect of the histamine on the deep vessels was furnished by Zsedenyi.<sup>18</sup> After ligation of the bleeding vessels in the course of an operation, histamine was applied to the skin adjoining the incision. Thereupon fresh bleeding occurred from the deep small vessels. This permitted an exact hemostasis.



Fig. 2.—Application of histamine by (left figure) the scratch method and by (right figure) cataphoresis.

#### CHOICE OF METHOD OF APPLICATION

The scratch method has the advantage of simplicity. However, the unequal distribution of the urticaria makes the method less effective than cataphoresis. The lesion of the skin opens the possibility of infection; systemic reaction may occur if the scratches are too deep, and the persistence of the scratches for about a week limits the application of the method.

Cataphoresis, on the other hand, requires an apparatus, but it is the method of choice. It is efficient and does not cause discomfort, and the cutaneous changes are transitory. Systemic reactions were not observed.

18. Zsedenyi, quoted by Kopits.<sup>7</sup>

The leaf, impregnated with histamine, as devised by Deutsch, offers the advantage of a stable, ready-to-use product, and it obviates the necessity of making up solutions, which deteriorate on standing. The disadvantage, however, is that the leaves come in one size, which is sometimes not sufficiently large to cover the entire affected part. I therefore still use the solutions of histamine on blotting paper cut to fit the required area.

Although I confined myself chiefly to the application of histamine by cataphoresis, the mechanical method has great value, as it proves that the action of histamine is independent of that of the galvanic current.

The problem of iontophoresis and its efficiency is therefore in no wise involved in the histamine therapy of rheumatic infections.

TABLE 1.—*Results of Histamine Therapy*

Diagnosis	Number of Patients	Cure or Improvement		Failure		Recurrence in Total Number of Cases
		Num- ber	Per Cent	Num- ber	Per Cent	
Myositis.....	376	343	91.2	33	8.8	33 (205)
Static and traumatic myositis.....	35	32	91.5	3	8.5	
Contractures.....	29	20	69.0	9	31.0	16
Arthritis.....	151	124	82.1	27	17.9	22 (51)
Peripheral and circular disturbances.....	24	20	83.3	4	16.7	
Neuralgias.....	45	31	64.6	17	35.4	8 (22)
Miscellaneous.....	67	40	59.7	27	40.3	6 (11)
Totals.....	730	610	83.5	120	16.5	55 (242)

## INDICATIONS AND THERAPEUTIC RESULTS

Table 1 presents a compilation of the collected data on treatment of rheumatic conditions with histamine, which includes 68 cases of my own observation. In a total of 730 cases, 610 patients (83.5 per cent) were either cured or improved: 120 (16.5 per cent) were not benefited. However, in a series of 342 favorable cases, reported by Deutsch and Kopits, Rosenblüth and me,<sup>19</sup> the relief was temporary in only 85 (24.8 per cent).

*Myositis (Myalgia).*—Three hundred and seventy-six cases, representing about 52 per cent of the total number published, belong to the group of myositis. The prevalence of myositis in the reports to date is explained by the short time that has elapsed since the introduction of

19. Kling, D. H.: Histamine Therapy of Rheumatic Affections and Disturbances of the Peripheral Circulation, *Ann. Surg.* 99:568 (April) 1934.

histamine, which permits a definite conclusion only in relatively acute conditions presenting a simple clinical picture.

Table 2 gives a résumé of the results of the various authors and shows that the percentage of cure or improvement lies between 75 and 98 per cent.

An analysis of 32 cases of my own observation is shown in table 3. The ages ranged from 23 to 67 years. Duration of the symptoms amounted to from one week to two years. Previous treatment was given without success in 6 cases and consisted of baking, massage,

TABLE 2.—*Résumé of Histamine Therapy of Myositis*

Author	Number of Cases	Cure or Improvement		Failures		Recurrence	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Deutseh <sup>6</sup> .....	94	89	95.7	5	4.3	14	16.7
Trumpf <sup>8</sup> .....	100	98	98.0	2	2.0		
Kopits <sup>7</sup> .....	57	56	98.2	1	1.8	12	21.9
Vas <sup>12</sup> .....	45	40	88.9	5	11.1		
Rosenblüth <sup>11</sup> .....	45	36	75.0	12	25.0	6	16.6
Kling <sup>10</sup> .....	32	24	75.0	8	25.0	1	3.1
Totals.....	376	343	91.2	33	8.8	33	11.2*

\* Of 205 cases recorded.

TABLE 3.—*Summary of My Material on the Administration of Histamine by Cataphoresis*

Condition	Number of Cases	Cure or Improvement		No Improvement	
		Number	Per Cent	Number	Per Cent
Myositis.....	32	24	75.0	8	25.0
Arthritic.....	24	14	58.3	10	41.7
".....	5	5	100.0		
".....	2	2			
Aeroparesthesia.....	3	2	....	1	
Buerger's disease.....	1	1			
Angioneurotic edema.....	1	1			
Total.....	68	49		19	

diathermy and injections. The muscles of the shoulder were affected in 23 cases; the arm and wrist in 2 cases each, and the forearm, neck, elbow and calf in 1 case each. Cure or improvement was achieved in 24 cases (75 per cent); 8 of the patients (25 per cent) remained unrelieved. No other treatment was given with the histamine therapy. The beneficial results, while lower, show, on the other hand, a smaller percentage of recurrences (3.1 per cent) than do the reports by other authors.

The diagnosis was based on pain, tenderness and limitation of motion due to muscle spasm. Sometimes distinct hardness could be palpated at the insertion in the muscle (myogelosis). In order to exclude pathologic conditions of the bones and joints, roentgenograms were taken in all cases of longer duration which were not readily amenable to treatment.

A thorough examination of all of the muscles of the affected part for pain, tenderness, contraction and nodules is of the utmost importance for success in the treatment. It is a common occurrence, for instance, for a condition to be diagnosed as myositis of the trapezius muscle when further examination would detect tenderness and spasm of the deltoid and pectoralis insertions as well. All affected muscles and the antagonists must be treated.

The effect of the treatment in favorable cases is rather striking. Immediately after the first application, pain and tenderness disappear, and motion is increased. If the initial effect is not pronounced, the final outcome must be viewed with skepticism. This analgesic effect lasts at first for several hours, corresponding to the aforementioned changes in the circulation. The treatment is therefore at first repeated daily, if possible; with the progress of the recovery, the painless intervals increase to twenty-four and forty-eight hours. Treatment is then repeated every second or third day, until all of the symptoms have disappeared. However, I was not able to give the patients at the clinic more than three treatments weekly. The number of treatments required varied from one to seventeen. In severe and chronic cases one is justified in continuing as long as there is a satisfactory and immediate response to the treatment.

*Muscular Conditions Following Trauma, Static Strain or Diseases of the Bones and Joints.*—Successful treatment of pain and muscle spasm following trauma was reported by several authors in a total of 35 cases, in 32 (81 per cent) of which the patients were cured or improved. This result, if confirmed in a large series, would present decided progress in the after-treatment of injuries to the extremities.

In static myalgia chiefly due to weak feet, Vas reported good results in 25 of 28 cases. In contractures of the muscles, due to pathologic conditions of the bones and joints, Kopits obtained improvement in 29 cases; however, in 16 cases the results were only transitory. Although the treatment in this group was only symptomatic, it could be employed to correct faulty position in preparation for final measures.

*Subacromial Bursitis.*—In 5 cases of subacromial bursitis, 4 of which showed deposits of calcium in the roentgenograms, I saw disappearance of pain and tenderness and return of complete motion after from four to fourteen treatments. In 3 of the cases previous treatment with diathermy and massage was not successful. If further observation in a large group of cases gives equally good results, cataphoresis should be the method of choice in subacromial bursitis.

I have also had good results in 2 cases of tenosynovitis of the extensor tendons of the hand.

*Arthritis.*—One hundred and fifty-one cases of different types of arthritic conditions were collected from the literature. Twenty-four cases of my own observation were included. Improvement was noted in 124 cases; the improvement was transient in 22. The results were inconclusive because of the small number of cases and the indefinite



nomenclature used. (Deutsch and Kopits referred to their cases as arthritis deformans and polyarthritis; Vas wrote of "diseases of the joints.")

The analysis of my 24 cases of arthritis is given in table 4. In 14 cases of osteo-arthritis of the knee joint, a diminution or loss of pain and tenderness and a slight increase in motion were seen in 8 cases (57 per cent). Improvement was noted in 2 cases each of infectious and traumatic arthritis and in 1 case of rheumatoid arthritis; in 5 cases of arthritis of the sacro-iliac joint the treatment failed in 4 instances. From this small amount of material I can submit only one conclusion, namely, that there is a difference in the effect according to the type and location of the arthritis; arthritis of the knee joint appears to react far more favorably than that of the sacro-iliac joint.

*Neuralgia.*—In 42 cases of neuralgia, 31 patients were reported improved; of these 17 were improved only transitorily. Deutsch experienced failure in 3 cases of neuralgia of the cutaneous femoris

TABLE 4.—*Analysis of Histamine in Arthritis*

Type of Arthritis	Number of Cases	Cure or Improvement		No Improvement	
		Number	Per Cent	Number	Per Cent
Osteo-arthritis (knee).....	14	8	57.1	6	42.9
Sacro-iliac (joint).....	5	1	20.0	4	80.0
Infectious.....	2	2			
Rheumatoid.....	1	1			
Traumatic.....	2	2			
Total.....	24	14	58.3	10	41.7

lateralis nerve; he regarded histamine as ineffective in pure neuralgia and improvement as an indication that the muscle was chiefly involved, especially in ischialgia.

*Acroparesthesia.*—Vas reported good results in 18 of 20 cases of acroparesthesia of the hands or feet. I have seen improvement in 2 of 3 cases of acroparesthesia in women of middle age who complained of numbness, hypersensitivity and paresthesias.

*Miscellaneous Conditions.*—Deutsch had complete failure as to permanent results in 10 cases of painful periostitis. Vas claimed success in 10 cases of furunculosis and in 3 cases of painful infiltrations after perivascular injections. Of considerable greater interest are his good results in a case of Raynaud's disease, in 2 cases of Buerger's disease and in 3 cases of chronic ulcer of the leg. I noticed improvement in 1 case of Buerger's disease and prompt cure after one treatment in 1 case of angioneurotic edema of the knee. The action of histamine in conditions of disturbed peripheral circulation requires extensive investigation.

#### COMMENT

With the exception of two authors, it is the consensus that the application of histamine by cataphoresis offers an efficient treatment of myositis. The two authors used faulty technic, applying the histamine

to only the painful spots; they neglected to treat the antagonists as well. Neither of the authors published figures of their results. Kauffmann's contention that the analgesic effect is due to the action of the positive pole and not the histamine is without foundation. In order to produce an effect by the galvanic current it is necessary, first, to apply it for a much longer time than one or two minutes and to use a stronger current than is used in applying histamine by cataphoresis. Secondly, the action of the histamine is not dependent on the application by cataphoresis. Its introduction by the scratch method or by intracutaneous, subcutaneous or intramuscular injections showed identical results. Ruhmann conceded to histamine only a counter-irritating effect like that of the application of capsicum. This analogy is only superficial. Both substances produce hyperemia. The diffuse irritation of the skin which is caused by a plaster of capsicum and which prevents repeated application of the plaster, is not produced by histamine, which has a selective action on the blood vessels. The skin returns to normal after several hours, and the histamine can be reapplied immediately.

Ruhmann overlooked further that the action of histamine has been thoroughly investigated and analyzed by scientific methods. Its dosage can be regulated, and its effect can be checked by accurate capillary microscopy, while other counter-irritants used empirically do not permit an accurate investigation.

In arthritis and vascular diseases histamine therapy is still problematic. One does not even know whether the technic used is entirely appropriate. It is possible that a more intensive method of treatment is necessary; I do not see any objection to the application of histamine by cataphoresis two or three times daily for patients in the hospital. Besides being practical, such continuous alteration in the circulation of the blood would be of great importance in the determination of the actual involvement of the peripheral circulation in arthritis. If the treatment is not efficient in itself, it could possibly be combined with other therapy.

#### SUMMARY

The application of histamine either by cataphoresis or by the scratch method is described.

The effect of this treatment consisted in a dilatation of the minute vessels and the smaller arterioles and in an increase in the flow of blood and in the permeability of the vessels, which caused a hyperemia and elevation of the cutaneous temperature of several hours' duration. Evidence was given of a longer duration of the capillary dilatation after considerable treatment (Bettmann).

The results in 730 cases collected from the literature are surveyed.

A definite conclusion as to the value of this method is at present possible only in myositis. Of 376 patients, 343 were cured or improved; recurrences were noted in 33 patients.

Thirty-two cases of myositis of my own observation are analyzed. In these cases 24 of the patients were cured or improved, and 8 remained unimproved.

Thorough examination and treatment of all of the affected muscles and their antagonists, are decisive for the success of the treatment.

Immediate relief of pain and tenderness after the first treatment was of favorable prognostic significance in this group.

Secondary myalgia due to static unbalance after trauma and strain was benefited in a moderate number of the cases reported.

Five patients with subacromial bursitis and 2 with tenosynovitis were successfully treated.

In 151 cases of arthritis reported in the literature, 124 of the patients were improved; in 22 cases the arthritis recurred.

In 24 cases of arthritis of my own observation, 14 of the patients were improved and 10 unimproved.

Long observation of extensive material, however, is necessary to draw definite conclusions as to the effect of the alteration of peripheral circulation by histamine in arthritic and vascular deficiencies.

NOTE.—Dr. Jerome Weiss, director of the department of physical therapy of the Hospital for Joint Diseases, Miss Acton and the staff carried out the treatments.

The patients were derived partly from the orthopedic services of Drs. Finckelstein and Frauenthal, Hospital for Joint Diseases, and partly from private practice.

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# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Renal Anomalies.*—Nordio<sup>1</sup> reported 2 cases of congenital ectopic pelvic kidney without any associated malformation of the genitals or of other parts of the body. In the first case, during an operation for retroverted uterus, the misplaced kidney was found at the right of the vertebral column and in the pelvic cavity. It was normal in size, without lobulation, slightly flattened and fixed; a fatty capsule was not apparent. As the kidney appeared to be functioning satisfactorily, it was left undisturbed. The patient, a woman who had borne seven children without unusual inconvenience, was seen one year later and was in excellent condition. This case indicates that a pelvic kidney which causes no disturbance or symptoms may go unrecognized throughout life.

The second case, before operation, was thought to be one of unilateral cystic tumor of the left adnexa uteri. As the ureter of the ectopic kidney was too short to permit nephropexy, nephrectomy was done, and the patient was relieved from all symptoms. Owing to the fact that the ectopic kidney was lobulated and embryonal, and, consequently, soft, it presented an almost cystic consistency on palpation, unlike that of a normal kidney.

Kirkland<sup>2</sup> reported a case of congenital absence of one kidney, ureter and suprarenal gland. The remaining kidney was pyonephrotic, an

1. Nordio, Augusto: Contributo allo studio degli errori diagnostici nella distopia renale pelvica in ginecologia, Riv. ital. di ginec. 15:221 (July) 1933.

2. Kirkland, Keith: Congenital Renal Aplasia, Complicated by Pyonephrosis of the Existing Kidney, M. J. Australia 2:351 (Sept. 9) 1933.

aberrant renal vein apparently being the obstructive factor. Catheterization of the patient, a woman, aged 36, revealed an empty bladder after anuresis of twenty-two hours. On cystoscopy, the right ureteral orifice could not be found. The catheter could be passed into the left ureter for 20 cm.; urine was not obtained. Operation revealed that the ureteropelvic juncture was sharply kinked by a posterior renal vein coming from the lower pole of the kidney; the lower third of the kidney, which was cystic, was drained. The case is of interest because of the aberrant vessel which made efficient emptying of the left kidney an impossibility, and also because of the large isolated pyonephrotic sac which apparently had been present for a number of years. The patient had successfully gone through three pregnancies with this defective renal system.

Gutierrez<sup>3</sup> stated that at present it is possible to distinguish between, and to identify accurately in advance of operation, three anomalies of the upper portion of the urinary tract which formerly were much confused and frequently were discovered only at necropsy, namely, hypoplastic kidney, renal aplasia and congenital absence of one kidney. The underlying cause of all three conditions is embryonic malformation or lack of proper development of the urinary organs during intra-uterine life, wherein either the kidney does not develop to its full extent or the wolffian duct of the mesonephron fails to produce a renal bud after the duct has reached the cloaca. In view of the fact that congenital anomalies of the kidney constitute about 40 per cent of all pathologic lesions of the organ, the importance of their clinical recognition becomes apparent. The most important points in preoperative diagnosis have been classified on the basis of 8 illustrative cases, in accordance with the principal clinicopathologic and cysto-uropyelographic observations.

The hypoplastic kidney is small or infantile, whereas the other kidney undergoes compensatory hypertrophy. Two types of hypoplastic kidney exist: One contains normally functioning renal parenchyma with both medullary and cortical substance but with diminution in size and deformation of the pelvis, and the other contains no pyramidal or cortical substance, barring a few rudimentary glomeruli and tubules which are visible only microscopically. The pelvis is rudimentary or hydronephrotic in this type, and the calices may be lacking. The ureter is patent in the hypoplastic kidney, urine is normally secreted, and renal function may be normal or diminished; there are also good excretion of urea and elimination of phenolsulphonphthalein. Pyelography and roentgenography reveal a hypoplastic organ. The danger of the finding lies in the fact that such an organ is incapable of undergoing compensatory

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3. Gutierrez, Robert: Surgical Aspects of Renal Agenesis, with Special Reference to Hypoplastic Kidney, Renal Aplasia and Congenital Absence of One Kidney, *Arch. Surg.* 27:686 (Oct.) 1933.

hypertrophy in the event of surgical removal of the other kidney. Such a kidney is from a sixth to a third the size of its mate, which is always hypertrophic. The chief diagnostic sign is marked decrease in function, both quantitative and qualitative, in comparison with the other kidney, when the latter is normally developed; in the event that the other kidney has undergone pathologic change, clinical evidence alone is misleading, and the necessary differentiation depends also on a correct interpretation of a bilateral pyelogram. If there is an insufficient concentration of opaque substance by the hypoplastic kidney, as shown in the intravenous pyelogram, an ascending pyelogram will be necessary. The differential urographic diagnosis must be borne in mind, since this condition may readily be confused with the lesions observed in secondary renal atrophy acquired through disease. It must also be distinguished from other common types of anomalies, such as double kidney, in which the upper portion of the pelvis alone is diminutive, and one may be misled if the double pelvis and ureters have not both been properly visualized.

Renal aplasia may be regarded as renal hypoplasia of an extreme degree, being distinguished from the latter by the fact that the rudimentary and diminutive structure supposed to be a renal organ is only a small mass of aberrant fibrous tissue which at no time has had any excretory function, although it may be formed, microscopically, of embryonic and sclerotic, or even calcified, glomeruli and tubules. Here again two types exist. In the first, the amorphous mass of renal tissue has a small renal artery coming from the aorta, although there is no evidence of a true renal pedicle, pelvis or ureter; a short rudimentary and functionless ureter, however, may be discovered in the course of a careful postmortem examination. It is thus an organ which has never shown any signs of existence in a true sense and has never accomplished any physiologic function, yet, owing to the presence of an artery, it can eliminate into the mass of tissue the intravenously injected opaque substance, and thus the presence of aberrant renal tissue may be revealed in the urogram. In the second type there is no renal artery but only small aberrant blood vessels anastomosing from the blood supply of the suprarenal gland; thus no shadow results from intravenous injection of the opaque medium. Moreover, although the pelvis and the upper portion of the ureter are absent, there is always evidence of a remnant of the functionless or obliterated ureter in the aplastic side of the urinary bladder. Clinically, the patient has no symptoms related to the urinary tract, the only complaint being pain in the lumbar region. Cystoscopy reveals a normal bladder and two normal ureteral orifices but, on the side of the aplastic kidney, the ureter is found to be a blind stump, after 4, 5 or 6 cm., having no connection with the fatty mass of sclerotic renal tissue; any fluid injected will regurgitate, making only a hypothetical

diagnosis possible. Following intravenous injection of an opaque substance, however, a few tiny patches of shadow may be seen in the roentgenogram where the substance enters the dilatations of the few rudimentary tubules present, which at necropsy will be found to contain a few drops of yellow fluid that may have the characteristics of urine. Histologic section of the specimen removed definitely reveals the presence of renal tissue with embryonic tubules and glomeruli. Areas of calcification or degeneration, to the extent in which cysts are formed, may be seen, as in polycystic kidney. The patients complain of pain on both sides of the abdomen. On the side of the aplastic kidney, the pain is due to remnants of renal tissue which have the irritant action of a foreign body, whereas on the other side, the overwork of the hypertrophied kidney leads to painful symptoms also. Surgical treatment in such cases must be along very conservative lines, consisting in the removal of the remnants of the aplastic kidney with as much of the pararenal fatty capsule as possible.

Like the two preceding anomalies, congenital absence of one kidney has been widely confused with atrophic kidney, fused kidney and also with the two types of malformation already discussed. Once again two types exist: The first is the type of the true solitary kidney, with complete absence of both kidney and ureter on the opposite side. It may be ectopic or in cross ectopic position, but there is only one ureteral orifice into the bladder, and one half of the trigon has not been developed. As a rule, there is some associated genital malformation as well. The second type is the solitary fused kidney, in which there is evidence of union of two nephroblastomas into one organ, with two pelves and two ureters which may open normally or abnormally into the bladder. The solitary single kidney is peculiarly subject to disease, and in the event that it is diseased the prognosis is fatal. The association of a pathologic process, such as parenchymatous nephritis, formation of stones, pyelitis and pyelonephritis, with a tendency toward hydronephrosis, oliguria, infection, anuresis and death, has commonly been recorded in the literature. Through errors in diagnosis, many operations have unwittingly been performed on the solitary single kidney, with fatal results.

The symptoms of these three conditions are insidious. Bilateral pain, with an enlarged palpable mass in one side of the abdomen, may signify hypertrophy of one kidney and demands careful urologic investigation of the upper portion of the urinary tract. Sole reliance should never be placed on the result of an intravenous pyelogram despite the brilliancy of the achievements of this new method, for it cannot be too strongly emphasized that in many cases bilateral retrograde pyelograms are indispensable.

Kemal,<sup>4</sup> writing from Constantinople, reported the case of a man, aged 30, who lived for twenty days with anuresis and practically symptomless uremia after the removal of an infected, calculous right kidney, which proved to be a solitary organ. The importation into Turkey of substances for intravenous use in urography is not permitted and, because of extraneous circumstances, retrograde pyelography also could not be carried out in advance of operation. In this case a stricture of the urethra made the introduction of a cystoscope impossible; therefore, Kemal made only an intramuscular injection of indigo carmine. Since the dye was eliminated after about fifteen minutes, he thought himself justified in concluding that there was a functioning left kidney and in performing nephrectomy. The coralliform shape and great size of the stone revealed at operation would have made its removal by nephrotomy impossible. The kidney, with a widely distended and infected pelvis, was about four times its normal size. On the first day after operation, when the catheter elicited only 10 cc. of a fluid which was mainly pus, the suspicion arose that the kidney which had been removed was solitary. This became a certainty when all measures undertaken to produce diuresis proved ineffectual. The temperature remained normal for five days, however, and the chlorides and the urea in the blood were only moderately increased. Even on the seventeenth day, the patient still felt well enough to inquire when he might be allowed to go home. He was found dead in his bed on the twentieth day, although he had been walking about the room only fifteen minutes before. Necropsy revealed only a barely visible rudiment of a left kidney, in which renal tissue could be seen microscopically. A left ureteral orifice in the bladder could not be found. The distended right ureter was filled only with pus.

[COMPILER'S NOTE.—Solitary single kidney is the condition in which one of the kidneys is definitely absent. The case reported by Kemal is not properly classified, since in the postmortem examination nephrogenic tissue was present as revealed by the naked eye and the histologic section of the mass removed. This case should have been reported as renal aplasia and not congenital absence of one kidney or solitary single kidney.]

*Tumors.*—Pascual<sup>5</sup> stated that tumors of the renal pelvis are not infrequent. Chronic inflammatory processes in the pelvic mucosa of all kinds, leukoplasia and continued irritation set up by a calculus seem to play an important part in the etiology. The chronic inflammatory

4. Kemal, M.: Entierrung einer Solitärniere. Symptomloser Verlauf einer 20 Tage währenden Urämie, *Deutsche med. Wchnschr.* 59:1398 (Sept. 8) 1933.

5. Pascual, Salvados: Los tumores de la pelvis renal, *Fifth Cong. Internat. Soc. Urol.*, 1933, p. 82.



factor cannot be a very important one because, if it were, it would be a frequent occurrence to find tumors of the renal pelvis accompany tuberculous processes of the kidney, which is not the case.

Histologically, the majority of tumors of the renal pelvis are of an epithelial nature; these are benign papillomas in some cases and malignant papillary epitheliomas in others. There are also nonpapillary epitheliomas of undoubted malignancy and a few nonepithelial tumors. The relative frequency with which these three types of new growth occur is approximately the same. Nonepithelial malignant growths are extremely rare. Pascual stated that in spite of the fact that it is possible to maintain a histologic distinction between benign and malignant tumors, clinically it is impossible to do so, partly because benign papillomas often degenerate into papillomatous epitheliomas, and partly because these tumors, even the most benign in appearance, owing to their tendency to spread, to metastasize and to generalize, enter into the clinical evolutionary picture of carcinomas and behave just like them.

Pascual stated that the most characteristic feature of tumors of the renal pelvis is their tendency to spread and to propagate within the remainder of the urinary tract, ureters and bladder, where they usually recur and maintain the original histologic type. The manner in which this type of propagation takes place is not definitely known; the mechanism is possibly multiform and may be that of contamination by urinary fluid. Some investigators consider the propagation to be direct, and a smaller group think that the lymphatic system may be responsible. Some also defend the hypothesis of concurrent formation of tumors in the pelvis, ureter and bladder.

Pascual reported that tumors of the renal pelvis present the classic signs of hematuria, increase in volume of the organ and pain (not of frequent occurrence or very characteristic) which generally accompany formation of tumor in the kidney, either in the pelvis or in the parenchyma. From the point of view of symptoms, it is extremely difficult to establish an exact diagnosis as to the situation of the tumor.

Pascual felt that tumors of the renal pelvis are always serious, even in cases of typically benign papilloma, in view of their tendency to propagate, to undergo carcinomatous degeneration and to become transitional forms. The histologically benign nature of the tumors does not exclude the possibility of diffuse metastatic implantation to ureters or bladder, and such metastasis may even be of a malignant nature. The prognosis in these cases is, therefore, serious on all occasions. Pascual concluded that, bearing all these factors in mind, treatment can be only surgical. It should consist of nephrectomy and ureterectomy, either partial or total, according to the surgical possibilities and the condition of the ureter.

Van den Branden<sup>6</sup> stated that there are two classes of tumors of the renal pelvis: epithelial tumors and tumors of mesodermic origin, the latter being extremely rare. Epithelial tumors are divided into three categories according to their pathologic anatomy: papillomas, papillary epitheliomas and sessile tumors. These may be divided into two classes in accordance with their clinical evolution: papillary tumors of a metastatic nature which invade the urinary mucosa and sessile tumors or true carcinomas with local development which penetrate neighboring tissues and are conducive to metastasis. Van den Branden stated that one can never say with absolute certainty that a papilloma is benign, the frequency of its dissemination rendering it dangerous. Nearly every benign papilloma is potentially malignant: although the process is sometimes slow, the development is fatal, death often being due to complications. The principal symptoms are hematuria and pain and a perceptible mass, the first appearing often early in the condition. Hematuria has intermittent characteristics and is likely to appear at any time independent of fatigue or effort. On the whole, it is painless and frequently accompanied by the passage of clots of blood. The mass is not due to the neoplasm proper but rather is the result of hydronephrosis. The increase in volume is more rapid than in renal carcinoma. Pain nearly always appears in the form of renal colic caused by distention of the renal pelvis.

The various types of treatment for this condition are: (1) Fulguration by the urethral route. (2) Resection of the lower portion of the ureter with ureteroneocystostomy. This operation, however, Van den Branden considered inadvisable as it leads to atrophy of the kidney. He suggested that an operation of a more drastic nature is to be preferred. (3) Nephrectomy with partial ureterectomy. With a single incision, that part of the ureter is removed which can be exposed by the usual incision for nephrectomy. This operation is indicated for sessile tumors in the upper part of the ureter or in the renal pelvis. The indication is justified by the fact that these tumors develop by continuity and not by dissemination. Van den Branden reported the following results: patients dying after operation for malignant tumor, 10 per cent: those having recurrence within one year, 64 per cent. and those surviving for more than three years without recurrence, 26 per cent. Of the latter, 3 of 58 had no recurrence in more than six years. In the case of papillomatous tumors, 65 per cent of the patients suffered recurrence in the ureter. Of the 26 patients reexamined, 6 had shown no sign of recurrence in more than three years. (4) Subtotal nephroureterectomy. This operation is performed in one or two stages; in any case, two incisions, one lumbar and one anterior, are made. Van

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6. Van den Branden, Fernand: *Tumeurs du bassinet et de l'uretère*, Fifth Congr. Internat. Sec. Urol., 1933, p. 139.

den Branden stated that it was preferable to leave a minimal interval of time between the two operations. This particular method, however, has not been used very often, the majority of surgeons preferring to complete the operation in one stage and in a more drastic manner. (5) Total nephro-ureterectomy with resection of the ureteral orifice. The frequency of grafts in the intramural part of the ureter indicates its excision. Complete removal complies entirely with all modern and leading principles of surgical treatment of tumor. The postoperative mortality rate is higher (22 per cent), but the final results obtained are of longer duration. An operation in two stages is better sustained, although it is advisable not to allow too long an interval to elapse between operations. Of 10 patients whose cases had been followed, 7 have survived for more than two years, of whom 2 are in perfect health five and a half and seven and a half years, respectively, after operation. The lower part of the ureter is difficult of access, good visibility for operating being difficult to achieve.

Joly<sup>7</sup> stated that epithelial tumors of the renal pelvis are distinctly rare when compared with neoplasms of the kidney itself. Statistics on this point vary greatly, but the average of those available is between 7 and 8 per cent. Epithelial tumors may be divided into two main groups: papillary and the solid growth. Each of these groups has been divided into two subgroups. Thus papillary tumors comprise (1) benign papillomas and (2) papillary carcinomas, whereas solid growths have been classified as (1) transitional cell carcinomas, if they arise from cells similar to those found in normal transitional epithelium, and (2) squamous cell carcinomas, which are formed of cells that have no counterpart in normal transitional epithelium.

Joly stated that papillary tumors are the most numerous, comprising three fourths of the whole series. Of 337 cases which he collected, the tumor was a benign papilloma in 120, a papillary carcinoma in 138, a transitional cell carcinoma in 29 and a squamous cell carcinoma in 50. In more than half the cases of papilloma, the patients were between the ages of 30 and 60, whereas in most of the cases of malignant growth the patients were between the ages of 40 and 70. With papillary tumors, no predisposing causes have been found. These tumors appear to originate in the pelvis of normal kidneys. With solid growths, stone and infection are important etiologic factors. This is most marked with squamous cell growths, more than half of which arise in cases of calculous pyonephrosis. The secondary changes in the kidney usually are due to back pressure; hematonephrosis is formed, with atrophy of the renal parenchyma due to this pressure. Solid tumors have a greater

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7. Joly, J. S.: *Epithelial Tumors of the Renal Pelvis and Ureter*, Fifth Cong. Internat. Soc. Urol., 1933, p. 211.

tendency to invade and replace renal tissue than villose tumors. Pyelography, Joly stated, is the only method by which the diagnosis of neoplasm of the renal pelvis could be definitely established. The symptoms of tumors of the renal pelvis resemble those of renal neoplasm so closely that it is impossible to distinguish them without the aid of a pyelogram. The treatment of villose tumor consists in removal of the kidney and ureter. Simple nephrectomy is so often followed by recurrences in the ureter that it should be abandoned. When the tumor is solid, nephrectomy with removal of the lumbar portion of the ureter usually is sufficient. The prognosis is very grave. A recurrence was found in approximately half of the cases of benign papilloma which were followed, and in about two thirds of the cases of papillary carcinoma. A "cure" has been obtained only rarely when the growth was solid. Tumors of the ureter are much less common than those of the renal pelvis. They are, however, similar in structure, and the same classification has been adopted. In 101 of 133 cases, the growth was papillary. In approximately half the cases, the neoplasm was found in the lower third of the ureter.

*Trauma.*—Luccioni<sup>8</sup> emphasized the importance of early diagnosis in cases of combined contusions of the spleen and left kidney, in order to make the correct incision with least destruction of the abdominal wall and with a minimum of operative shock. Such an association of lesions increases the seriousness of the prognosis, and in unfavorable cases death ensues rapidly. In Luccioni's case, however, the patient lived until the sixth day despite rupture of the spleen, of the left kidney and of the tail of the pancreas. Goinard reported a mortality rate of 50 per cent in such conditions; Lathuraz-Violet, 66.6 per cent, and Fiolle, 71.4 per cent. Without surgical intervention, the mortality rate is 100 per cent. Diagnosis of the splenic rupture is essential, since this necessitates immediate operation, whereas repair of the renal lesion is less urgent. Signs of internal hemorrhage usually are evident, and the pulse should be watched carefully. There may be violent pain in the left side, although lumbar pain may predominate. The abdominal wall is contracted, especially in the left upper quadrant. Hematuria is marked, usually from the first urination. A perirenal hematoma may be felt on palpation. The condition usually requires immediate surgical intervention too urgent for cystoscopy, urethral catheterization or, even, intravenous pyelography.

There are several different incisions, but the best, as Luccioni stated before, will be that one which, reduced to a minimum for easy cases, can be readily transformed into a wide approach without excessive muti-

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8. Luccioni, Francois: Étude de voies d'abord combinées dans les plaies et dans les contusions de la rate et du rein gauche, Arch. d. mal. d. reins 7:261, 1933.

lation of the abdominal wall. It must give a wide view of the left kidney and of the spleen and expose their pedicles. The main consideration is to accomplish satisfactory hemostasis. Lastly, the incision should not destroy innervation of the abdominal wall and should minimize cutting of muscles. Luccioni has chosen supra-umbilical, median laparotomy, with which there may be combined, in case of need, the horizontal incision of Bazy, the oblique incision of Rio-Branco (upward to the left from the umbilicus), that of Sprengel (downward obliquely to the left from the tip of the sternum), that of Lecene (more vertically upward to the left from the umbilicus) or the dorsolumbar incision of Fiolle. Luccioni preferred Fiolle's incision to the rest because, with no greater destruction of the abdominal wall than with the other incisions, it permits easier splenectomy and nephrectomy as well as inspection of the tail of the pancreas.

Very rarely is conservative treatment of the spleen possible, and partial splenectomy is always hazardous. The renal lesion demands the same treatment as an isolated contusion of the kidney. Total nephrectomy should be done only if the vessels of the pedicle are torn or the parenchyma is crushed into several fragments. If one pole of the kidney is torn apart, partial nephrectomy should be attempted; in other cases, suture, or even tamponade, or these two combined, may be indicated. Drainage of the bed of the spleen will, as a rule, be unnecessary when hemostasis is perfect, but drainage of the renal region will usually be indicated on account of the separation produced by the perirenal hematoma. Fiolle's method has the further advantage of permitting drainage at the lowest gravitational point without supplementary procedures. The incision starts at the axillary line and follows the costal border backward along the lower border of the eleventh and twelfth ribs, encroaching slightly on the lumbar mass. Both the kidney and the spleen are accessible by this route, and it permits extraperitoneal approach to the kidney. It cuts the eleventh and twelfth intercostal nerves, but spares the ninth. It is therefore not destructive and permits ready reconstruction of the abdominal wall.

*Stones.*—Walters<sup>9</sup> stated that removal of branched stones filling the pelvis and calices of one or both kidneys frequently has been delayed until symptoms of renal infection or obstruction, with partial renal insufficiency, developed. After a decision has been reached as to the advisability of removing such stones, the question arises as to whether to remove them by pelviolithotomy or by a long incision in the convex portion of the kidney, splitting the kidney practically in two portions and thus extracting the stone. Walters reported that his experience with

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9. Walters, Waltman: Removal of Branched Stones from the Kidney, *Proc. Staff Meet., Mayo Clin.* 8:468 (Aug. 2) 1933.

the latter method has led him to believe that it is impracticable because of the serious bleeding that occurs. Therefore, he has used a combination of pelvolithotomy and nephrolithotomy, retracting the renal parenchyma from the pelvis in order to make a larger incision. He stressed the value of this procedure because, if patients have little extrarenal pelvis, it is impossible to retract the renal parenchyma which overlies the intrarenal portion of the pelvis for a distance of 1 or 1.5 cm. and sometimes more, so that, frequently, the division of the pelvis into its calices cannot be visualized. After as much of the stony material as possible has been removed through the pelvis, and that usually means all but the piece or pieces in the calices, a small opening is made over each calix and the remaining portion of the stone is removed by a combination of pelvolithotomy and nephrolithotomy. Bleeding from openings in the renal parenchyma can be controlled perfectly by the introduction of the Pezzer catheters to be used for temporary drainage.

Bliss, Livermore and Prather<sup>10</sup> studied the relation of vitamins to the formation of calculi. They used rats, which normally are free from urinary calculi; calculi developed in these rats only when they were given deficient diets. The results obtained in this study indicate that an insufficiency of vitamin A in the diet may be a factor in the formation of urinary calculi in rats. In 34 rats of a group of 55 (61.8 per cent) which had been given a diet devoid of vitamins A and D, urinary calculi developed, whereas examination of 32 animals of a group of 56 (57.1, per cent) given a diet devoid of vitamin A revealed stones or sand. From forty to seventy days are required for calculi to form in the urinary bladder of rats. The urinary calculi found during this study were composed mainly of calcium and magnesium phosphates.

Kretschmer<sup>11</sup> reported 3 additional cases of cystinuria and cystine stones. He stated that, except for the complications attendant on the formation of cystine calculi, cystinuria usually is considered a harmless anomaly. It is a well recognized clinical fact that among many persons who have cystinuria for many years, or for a lifetime, calculi may never develop, whereas in others who do not have cystinuria, calculi develop. It is when disease due to a calculus develops that cystinuria becomes of clinical importance.

Kretschmer stated that the question of visibility of the cystine calculus in the roentgenogram is still far from settled. Thus, Holmes and Ruggles stated that the order of visibility of urinary stones is as follows: phosphate and cystine stones, very dense; oxalate stones, next, and urate

10. Bliss, A. R., Jr.; Livermore, G. R. and Prather, E. O., Jr.: The Relation of Vitamin A and Vitamin D to Urinary Calculus Formation, *J. Urol.* 30:639 (Dec.) 1933.

11. Kretschmer, H. L.: Cystinuria and Cystin Stones, *J. Urol.* 30:403 (Oct.) 1933.

lation of the abdominal wall. It must give a wide view of the left kidney and of the spleen and expose their pedicles. The main consideration is to accomplish satisfactory hemostasis. Lastly, the incision should not destroy innervation of the abdominal wall and should minimize cutting of muscles. Luccioni has chosen supra-umbilical, median laparotomy, with which there may be combined, in case of need, the horizontal incision of Bazy, the oblique incision of Rio-Branco (upward to the left from the umbilicus), that of Sprengel (downward obliquely to the left from the tip of the sternum), that of Lecene (more vertically upward to the left from the umbilicus) or the dorsolumbar incision of Fiolle. Luccioni preferred Fiolle's incision to the rest because, with no greater destruction of the abdominal wall than with the other incisions, it permits easier splenectomy and nephrectomy as well as inspection of the tail of the pancreas.

Very rarely is conservative treatment of the spleen possible, and partial splenectomy is always hazardous. The renal lesion demands the same treatment as an isolated contusion of the kidney. Total nephrectomy should be done only if the vessels of the pedicle are torn or the parenchyma is crushed into several fragments. If one pole of the kidney is torn apart, partial nephrectomy should be attempted; in other cases, suture, or even tamponade, or these two combined, may be indicated. Drainage of the bed of the spleen will, as a rule, be unnecessary when hemostasis is perfect, but drainage of the renal region will usually be indicated on account of the separation produced by the perirenal hematoma. Fiolle's method has the further advantage of permitting drainage at the lowest gravitational point without supplementary procedures. The incision starts at the axillary line and follows the costal border backward along the lower border of the eleventh and twelfth ribs, encroaching slightly on the lumbar mass. Both the kidney and the spleen are accessible by this route, and it permits extraperitoneal approach to the kidney. It cuts the eleventh and twelfth intercostal nerves, but spares the ninth. It is therefore not destructive and permits ready reconstruction of the abdominal wall.

*Stones.*—Walters<sup>9</sup> stated that removal of branched stones filling the pelvis and calices of one or both kidneys frequently has been delayed until symptoms of renal infection or obstruction, with partial renal insufficiency, developed. After a decision has been reached as to the advisability of removing such stones, the question arises as to whether to remove them by pelviolithotomy or by a long incision in the convex portion of the kidney, splitting the kidney practically in two portions and thus extracting the stone. Walters reported that his experience with

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9. Walters, Waltman: Removal of Branched Stones from the Kidney, Proc. Staff Meet., Mayo Clin. 8:468 (Aug. 2) 1933.

the latter method has led him to believe that it is impracticable because of the serious bleeding that occurs. Therefore, he has used a combination of pelviolithotomy and nephrolithotomy, retracting the renal parenchyma from the pelvis in order to make a larger incision. He stressed the value of this procedure because, if patients have little extrarenal pelvis, it is impossible to retract the renal parenchyma which overlies the intrarenal portion of the pelvis for a distance of 1 or 1.5 cm. and sometimes more, so that, frequently, the division of the pelvis into its calices cannot be visualized. After as much of the stony material as possible has been removed through the pelvis, and that usually means all but the piece or pieces in the calices, a small opening is made over each calix and the remaining portion of the stone is removed by a combination of pelviolithotomy and nephrolithotomy. Bleeding from openings in the renal parenchyma can be controlled perfectly by the introduction of the Pezzer catheters to be used for temporary drainage.

Bliss, Livermore and Prather<sup>10</sup> studied the relation of vitamins to the formation of calculi. They used rats, which normally are free from urinary calculi; calculi developed in these rats only when they were given deficient diets. The results obtained in this study indicate that an insufficiency of vitamin A in the diet may be a factor in the formation of urinary calculi in rats. In 34 rats of a group of 55 (61.8 per cent) which had been given a diet devoid of vitamins A and D, urinary calculi developed, whereas examination of 32 animals of a group of 56 (57.1 per cent) given a diet devoid of vitamin A revealed stones or sand. From forty to seventy days are required for calculi to form in the urinary bladder of rats. The urinary calculi found during this study were composed mainly of calcium and magnesium phosphates.

Kretschmer<sup>11</sup> reported 3 additional cases of cystinuria and cystine stones. He stated that, except for the complications attendant on the formation of cystine calculi, cystinuria usually is considered a harmless anomaly. It is a well recognized clinical fact that among many persons who have cystinuria for many years, or for a lifetime, calculi may never develop, whereas in others who do not have cystinuria, calculi develop. It is when disease due to a calculus develops that cystinuria becomes of clinical importance.

Kretschmer stated that the question of visibility of the cystine calculus in the roentgenogram is still far from settled. Thus, Holmes and Ruggles stated that the order of visibility of urinary stones is as follows: phosphate and cystine stones, very dense; oxalate stones, next, and urate

10. Bliss, A. R., Jr.; Livermore, G. R., and Prather, E. O., Jr.: The Relation of Vitamin A and Vitamin D to Urinary Calculus Formation, *J. Urol.* 30:639 (Dec.) 1933.

11. Kretschmer, H. L.: Cystinuria and Cystin Stones, *J. Urol.* 30:403 (Oct.) 1933.



stones, least dense. Harris stated that older reports in which it was stated that cystine stones were not opaque are erroneous, and according to Lewis, the general opinion seems to classify the stones as shadow-casting (often faint). Thomas and Roda are also of the opinion that cystine stones cast a distinct shadow. Hicks said that small cystine stones are only slightly, or not at all, opaque to roentgen rays and, consequently, this means of diagnosis is not important in their detection. It would seem, therefore, that among patients with a history of renal colic whose urine contains crystals of cystine or who give a positive reaction to the test for cystine and a negative roentgenogram, repeated examination with the wax-tipped catheter is in order. Kretschmer stated that the treatment of cystine stones does not differ from that of any other type of stone in the urinary tract, and that most investigators agree that the treatment of choice is surgical. It has been known for a long time that cystine is soluble in an alkaline solution, and the administration of alkalis is recommended, not only to cause disintegration of a stone, but also to prevent the formation of stones in cystinuric persons, or to prevent the recurrence of stones after such patients have been operated on. Because of the tendency of this type of stone to recur, the value of surgical treatment has been questioned, and attempts have been made to produce disintegration of the stone by the internal administration of alkalis.

Walters and Castleton<sup>12</sup> stated that the greatest problem is not surgical removal of cystine calculi, but prevention of their recurrence. Cystine is a complicated organic compound belonging to a group of amino-acids, and is the only compound in this group that contains sulphur. Normally, cystine originates from catabolism of protein, either endogenous or exogenous. Normally, also, there is a trace of cystine in the urine, averaging 4 mg. per hundred cubic centimeters. Crystals are not found normally. In cystinuria, there is usually about three times that amount, and crystals may or may not be present. Cystine may be found in the urine in the form of hexagonal, colorless, highly refractile crystals, or in the form of needles. In alkaline urine, crystals are not found, the cystine remaining in solution. Cystine stones are yellowish and waxy, with a somewhat semitransparent luster. They may be of any size, and cases have been recorded in which the stones weighed 50 Gm. They may be pure cystine, or they may contain admixtures of other urinary constituents. The finding of crystals of cystine in the urine determines the diagnosis of cystinuria. However, as noted previously, cystinuria may be present without the crystals.

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12. Walters, Waltman, and Castleton, K. B.: Cystine Renal Calculus, *West. J. Surg.* **41**:622 (Nov.) 1933.

Walters and Castleton stated that if crystals of cystine are present in the urine, it does not mean that calculi are present. They stated that many cases are known, especially those of relatives of patients who had cystine stones, in which crystals of cystine had been present in the urine for many years without any evidence of formation of stone. Patients of any age may be affected. They said that there is a difference of opinion concerning the visibility of cystine stones in roentgenograms. In some cases the stones have been shown clearly. Cystine calculi rarely are pure, and, if they contain a considerable amount of calcium, they may cast a clear shadow. In the past, treatment has been discouraging and unsatisfactory owing to the tendency toward recurrence of the calculi. The new dietary control of the urinary reaction will be a great improvement in the future. The first, and usually the simplest, step is removal of the stone. The main problem is prevention of recurrence, and for this purpose a diet low in protein and constant alkalization of the urine have long been recommended.

*Tuberculosis.*—Lieberthal and Huth<sup>13</sup> stated that the normal kidney does not excrete bacilli of tuberculosis. These bacilli in the separated renal urine always come from the caseous centers of disintegrated tuberculous lesions which are in open communication with the renal pelvis. Tuberculous lesions in the kidney often are accompanied by a variety of secondary nontuberculous degenerative, inflammatory or sclerotic changes. In Lieberthal and Huth's opinion, the inflammatory foci described by various investigators as tuberculous nephritis are secondary nontuberculous inflammatory changes. Bacilluria in these cases unquestionably is caused by undiscovered minute ulcerative tuberculous lesion of the kidney. Nephrosis may develop as the result of pulmonary tuberculosis. The occasional appearance of glomerulonephritis in such cases is due to secondary infection of the tuberculous pulmonary cavities. The bacillus of tuberculosis or its toxins does not produce nephritis.

Lieberthal and Huth stated that in the presence of such an incipient ulcerative tuberculous lesion in the kidney the separated renal urine may not contain pus cells, the kidney may reveal no functional defect, and the bladder may be normal on cystoscopic examination. Such early lesions occasionally may heal and, in the author's opinion, they are responsible for the transient tuberculous bacilluria which sometimes is observed.

Henline<sup>14</sup> reviewed the literature and reported 97 cases in which nephrectomy had been performed for tuberculosis. In 34 cases the original symptoms complained of were: symptoms referable to the blad-

<sup>13</sup> Lieberthal, E., and Huth, Theodore: Tuberculous Nephritis and Tuberculous Bacilluria, *J. Urol.* **30**:153 (Aug.) 1933.

<sup>14</sup> Henline, R. B.: Renal Tuberculosis: Diagnosis and Treatment with a Study of 97 Cases of Nephrectomy for Tuberculosis, *Surg., Gynec. & Obst.* **57**:231 (Aug.) 1933.

der. 85.3 per cent; pain in the kidney, 76 per cent; cloudy urine, 50 per cent; hematuria, 44 per cent, and general symptoms, 35 per cent. Henline stated that the diagnosis is established primarily by pyelographic observations, with evidence of a decrease in renal function in advanced cases. Intravenous urography is a distinct aid in some cases but cannot replace pyelography. Bilateral pyelograms should be made as a routine measure, if the ureters can be catheterized.

Henline said that nephrectomy followed by proper medical treatment offers the only hope of arresting destructive unilateral renal tuberculosis. As much of the ureter should be removed as is possible through the renal wound. Nephrectomy should be performed in those cases in which a destructive lesion in one kidney is manifest with good function of the remaining kidney, that is, when the second kidney can be shown pyelographically to be only slightly, if at all, affected. The operative mortality rate was approximately 3 per cent, and it was highest among young patients. Henline concluded his article by stating that medical care is an essential part of the treatment of renal tuberculosis and should be carried out by one thoroughly familiar with this work.

Seidman<sup>15</sup> cultured 89 tuberculous specimens (81 of which were urine from the bladder or the kidney) from 45 patients; bacilli of tuberculosis were isolated from 60, or 67.4 per cent, of the specimens, and from 39, or 86.6 per cent, of the patients. With 14 of the positive cultures, no acid-fast bacilli had been seen in the direct smear of concentrated sediment. From 14 specimens, in connection with which acid-fast bacilli had been seen in the direct smear, no growth was obtained. Fifteen specimens in which both cultures and direct smear were negative produced tuberculosis in guinea-pigs on inoculation. Seidman stated that a growth of bacilli of tuberculosis was obtained on Corper's crystal violet potato cylinder from 54 per cent of the positive sediments, on Petroff's coagulated egg medium from 69.1 per cent and on Sweany's milk, meat infusion, egg and cream medium from 71.6 per cent. Corper's potato medium is more satisfactory than these results indicate.

In this study, Seidman found that the shortest interval for primary isolation of bacilli of tuberculosis by culture was sixteen days. Growth was obtained within three weeks from 18.3 per cent of the positive specimens, in 7 per cent of the inoculated culture tubes. Inoculation of guinea-pigs still appears to be superior to cultures for the diagnosis of tuberculosis in cases in which the condition is suspected.

*Polycystic Disease.*—Braasch and Schacht<sup>16</sup> collected data from 193 cases seen at the Mayo Clinic in which the diagnosis had been poly-

15. Seidman, L. R.: Routine Culture of Urine for Tubercle Bacilli, *J. Urol.* **30**:195 (Aug.) 1933.

16. Braasch, W. F., and Schacht, F. W.: Pathological and Clinical Data Concerning Polycystic Kidney, *Surg., Gynec. & Obst.* **57**:467 (Oct.) 1933.

cystic kidney. Many of the patients returned for subsequent examination, and it was possible to confirm clinical data previously obtained. In this group were included 85 patients who were operated on for various renal complications occurring with polycystic disease, or who disclosed abnormal renal conditions in the course of operation for other abdominal lesions. Records of necropsy made at the clinic were available in 9 cases, and operative specimens were obtained in 10; therefore, histologic studies were possible in 19 cases. In addition, the observations made at postmortem examination were available in many cases in which death occurred after the patients had returned to their homes. The incidence of congenital polycystic kidney as found at postmortem examination at the Mayo Clinic was 9 in 9,171 cases, or a ratio of 1:1,019. The incidence noted clinically was 193 in 680,000 registrations, or 1:3,523.

Braasch and Schacht stated that the average age of patients at the onset of symptoms was 38.8 years. The average duration of life of patients reported dead had been fifty years. There was definite evidence of a hereditary trend. A systolic blood pressure of 145 mm. of mercury or more was found in 61 per cent of the cases, and the diastolic blood pressure was more than 90 mm. in 55 per cent. Laboratory evidence of renal insufficiency was present in more than 60 per cent of the cases. Surgical complications occurred in approximately 30 per cent.

The most common symptom was dull pain, usually in either renal region. Urinary symptoms of moderate frequency and dysuria often were observed. Gross hematuria occurred in approximately 33 per cent of cases and sometimes simulated that occurring with neoplasm. The first clinical symptoms were frequently those of renal insufficiency, although a remarkable degree of tolerance often was noted in the presence of advanced renal destruction. The prognosis varies largely with the degree of renal dysfunction. If renal function remains normal, the prognosis is good; even moderate reduction of renal function may remain stationary for as many as ten or fifteen years. Expectancy of life will average almost fifty years, although patients frequently are observed who are more than 60 years of age. The hereditary nature of the disease should discourage the bearing of children, and sterilization should be considered.

Meland and Braasch<sup>17</sup> stated that "multilocular cyst of the kidney" refers to a collection of cysts within a cyst. They expressed the belief that such cysts form a separate entity. There were 6 cases classified as instances of multilocular cyst on record at the Mayo Clinic, and they were being reported as examples of true multilocular cyst; 4 other examples were noted from the literature. In 3 cases of multilocular

<sup>17</sup> Meland, E. L., and Braasch, W. F.: Multilocular Cysts of the Kidney. *J. Urol.* 29:505 (May) 1933.

cysts seen at the clinic, the condition was found incidentally at post-mortem examination. None of the patients had had symptoms referable to the urinary tract. In the other 3 cases seen at the clinic, as well as in the 4 included from the literature, operation was performed, and in all cases evidence was present which directed surgical attack on the kidney.

The 6 cases seen at the clinic were reported in detail, and these, together with the reports of the 4 cases in the literature, indicated that the cysts vary in size from 3.5 by 4 cm. to 9 by 10 cm. The number of cystic cavities varied from 3 to 4 to several dozen (in 2 cases). The cavities were separated by complete septums in all three cases. Microscopically, the cysts were identical with solitary serous cysts. The walls of the cysts were composed of compact fibrous tissue in 9 cases. Remnants of renal tubules and glomeruli were present in the walls of the cysts in 4 of the cases seen at the clinic. In 8 of the cases there was a definite epithelial lining, columnar in 3, cuboidal in 2 and flattened in 3. In 2 cases there was no lining epithelium. There was definite evidence of atrophy from pressure in the region adjacent to the cyst in 4 cases. Of the 9 cases in which the kidney was available for study, the renal substance was normal in 5; in 2 there was evidence of chronic slight glomerulonephritis, and in 1 the kidney was normal except for the presence of many small cysts.

Meland and Braasch stated that 2 patients sought medical advice because of a noticeable tumor, and that 2 had pain in the renal region, a palpable tumor being discovered at the time of examination. One patient had had repeated renal colic on the left side and a functionless left kidney; the absence of function was due to an impacted ureteral stone. Meland and Braasch further stated that multilocular cysts and solitary serous cysts have several features in common: Both are unilateral; the walls of the cysts are identical in structure; both involve similar and localized regions of the kidney, and the symptoms of both depend on the size and the situation of the cysts.

*Nephropexy.*—Mathé<sup>18</sup> reviewed the history of nephropexy, pointing out its popularity at the end of the last century, at which time surgical suspension of the kidney had been perfected to the point that the percentage of failures had been reduced to a minimum. Many surgeons, eager to follow the new fashion, little heeded the criteria for operation advised by sane-thinking urologists, namely, pain, obstructive phenomena, persistent infection and gastro-intestinal symptoms, and they fixed movable kidneys that were causing no symptoms. Others employed methods that did not give lasting fixation. The result was that in many

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18. Mathé, C. P.: *Nephropexy: Present Day Status and Description of New Technique*, Surg., Gynec. & Obst. **57**:538 (Oct.) 1933.

instances operation gave little relief because it had been improperly done and because it had been depended on to relieve renal obstruction that did not exist. This led many surgeons to give up nephropexy, and thus the pendulum swung far and wide to such an extent that the patient in Dietl's crisis, owing to strangulation of a movable kidney, had difficulty in obtaining surgical relief. Mathé pointed out that nephropexy is still held in disrepute by certain surgeons and urologists, who emphasize the failure of this operation in cases in which, as usual, it has been wrongly applied, and who wilfully or blindly fail to recognize its beneficial results in numerous other cases. Many urologists are correctly performing nephropexy. The correct application of this procedure has been due to the development of urography, by means of which renal ptosis, ureteral angulation and changes in the kidney due to back pressure can be demonstrated.

Mathé described a new technic for surgical suspension of the kidney by means of its fibrous capsule, by which a satisfactory high suspension can be achieved and maintained, the height of suspension regulated and lasting fixation assured in a position that will maintain good drainage of urine and relief from symptoms. This consists of taking twenty day triangular chromic catgut sutures in the upper pole, in the middle region or in the junction of the middle region and lower pole, depending on the height of fixation desired. Suspension at a greater height can be obtained by placing these sutures lower in the kidney. The sutures are passed through the musculature above the twelfth, and sometimes the eleventh, rib by means of a Reverdin needle. In this way high fixation of the kidney is obtained, thereby taking up any slack that may exist in the ureter and assuring the straightening of any kinks which may be present. A third, similar triangular suture is taken in the posterior surface of the kidney in the region of the lower pole, and this is anchored to the musculature below the twelfth rib in order to steady the kidney and to prevent torsion or lateral displacement. Mathé emphasized three important steps which are usually necessary for successful nephropexy: ureterolysis, renal sympathectomy and partial decapsulation. Ureterolysis is always performed, by which the upper portion of the ureter is dissected free from the surrounding structures, as a routine measure, in order to eliminate any pressure that may be exerted thereon by aberrant vessels, or a fibrous band, which, left untouched, may defeat the purpose of the operation. Renal sympathectomy is employed only in cases presenting pain. Partial decapsulation is carried out when there is concomitant perinephritis in which the fibrous capsule of the kidney consists of a thickened, indurated, sclerotic shell. Lasting suspension is obtained by removing all fat between the kidney and the posterior and superior walls of the renal fossa and by keeping the patient in bed in the Trendelenburg position for three weeks.

The results obtained from this method in numerous cases were very satisfactory. Routine postoperative pyelographic study demonstrated that the kidney was permanently fixed in a sufficiently high position to free the ureter from kinks, and the results from the employment of this method thus surpassed those of all other methods formerly employed by Mathé.

*A New Surgical Technic.*—Lowsley and Bishop<sup>19</sup> stated that flat ribbon gut may be used successfully for the purpose of closing wounds in the renal cortex without inserting a needle or suture through the renal substance. A wound in any part of the renal cortex may be repaired by this method. The ribbon gut can be held in the proper situation by means of small loops of fibrous capsule. This method of closing a wound in the renal cortex is an acceptable surgical procedure, because it provides adequate approximation and results in satisfactory anatomic repair of the kidney; it is also compatible with life and health.

*Stasis.*—Rose and his associates,<sup>20</sup> from an analysis of 385 pyelograms and histories, found evidence that a renal pelvis which generally would be accepted as normal can be so shaped and so related to the parenchyma as to interfere with the free flow of urine, either in the entire pelvis or in a portion thereof. Such a renal pelvis is termed "dysuric." The analysis of pyelograms on the basis of dysuric factors gives functional individuality to all renal pelvises and ureters.

Rose and his associates stated that the final importance of such a condition in the pelvis lay in the fact that, in permitting urinary stasis, calculi are formed, infection is incited and continued and idiopathic hematuria and nephralgia may result. The facts given are of value in defining the etiology, in instituting and continuing treatment and in determining the prognosis in renal disease.

*Pneumonephrosis.*—Mathé and de la Pena<sup>21</sup> reported a case of a rare disorder of the kidney known as pneumonephrosis. It occurred in a case in which the formation of an advanced stricture completely occluded the lower portion of a ureter, resulting in hydro-ureter and hydronephrosis. Infection of the resulting closed sac by colon bacilli resulted in huge distention of the pelvis by pus and gas, entirely destroying the upper portion of the double kidney in which it occurred. The patient presented characteristic symptoms, and the condition was diag-

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19. Lowsley, O. S., and Bishop, C. C.: A New Method of Repairing Kidney Wounds, *Surg., Gynec. & Obst.* **57**:494 (Oct.) 1933.

20. Rose, D. K.; Hamm, W. G.; Moore, S., and Wilson, H. M.: Kidney Pelvises; Normal Variations in Their Shape and Flow with Possible Pathologic Significance, *Surg., Gynec. & Obst.* **57**:1 (July) 1933.

21. Mathé, C. P., and de la Pena, E.: Pneumonephrosis: Report of Case. *Urol. & Cutan. Rev.* **37**:732 (Oct.) 1933.

nosed by a characteristic roentgenographic picture; the diagnosis was proved by operation, and relief was obtained by a two-stage nephrectomy.

Mathé and de la Pena emphasized and recommended the employment of two-stage nephrectomy for patients weakened and debilitated by the toxic effects of encapsulated renal or perirenal infection. In their case, the first stage, consisting of incision and drainage, permitted the patient to regain his strength and to recover from the effects of toxic and pressure symptoms, thus assuring successful performance of the second stage of the operation, which consisted of extirpation of the diseased kidney.

#### PERIRENAL ABSCESES

Vermooten<sup>22</sup> stated that acute suppurative perinephritis (perinephritic abscess) secondary to bacterial (staphylococcic) emboli in the end arteries of the perinephrium is a definite clinical entity and need not have any relation to the kidney, except for the fact that the perinephrium happens to surround that organ. This disease is merely one of the end-results of staphylococcic bacteremia or septicemia. Metastatic staphylococcic abscesses, which develop from staphylococcic emboli, occur not only in the kidney and all the various organs of the body, but they also may and probably do occur in the perinephrium on one or both sides, resulting in acute suppurative perinephritis or perinephritic abscess. The abscess resolves readily with simple incision and drainage. These metastatic abscesses in the kidneys are practically always bilateral. They may occasionally be associated with a similar lesion in the perinephrium, and at times one or more of them may ulcerate through the renal capsule and form a secondary or perinephric abscess.

Vermooten stated that this lesion is a disease of the perinephrium, which is substantiated by the absence of pus cells in the urine in the majority of the cases of staphylococcic perirenal abscesses, the prompt subsidence of symptoms after incision and drainage of the abscesses, the common finding of a normal kidney partly or wholly surrounded by pus at the time of operation and the similar finding at necropsy. Vermooten concluded that this perinephric lesion can be distinguished from a true perinephritic abscess by the presence in a case of the latter type of pus and organisms in the urine, the persistence of these inflammatory products after drainage of a perirenal abscess, the long continued draining sinus or the formation of a urinary sinus after incising and draining one of these abscesses, the presence of calculous or tuberculous disease of the kidney, the occasional finding of a large solitary abscess of the kidney at operation and the common finding of multiple bilateral renal abscesses at necropsy.

22. Vermooten, V.: The Mechanism of Perinephric and Perinephritic Abscesses, *J. Urol.* 30:181 (Aug.) 1933.



## URETER

*Stone.*—Rolando<sup>23</sup> noted that a calculus may remain months or years in a ureter without doing great harm or causing great pain. The tendency today is to limit the operative treatment to as little as possible. Operation by the classic incision is simple, sure, and may often be done quite rapidly.

To establish the position of the stone, Rolando makes a ureterogram with the patient in the Trendelenburg position, and repeats the procedure immediately before operation. He recommends the wearing of a pair of cotton gloves outside of the rubber gloves, since in these cases excessive lubrication constitutes a disadvantage. When the stone is juxtavesical, it can be displaced upward by a finger in the vagina or the rectum. An assistant should be instructed how to do this, as it simplifies and shortens the operation. The incision begins about 4 cm. above the anterosuperior iliac spine and extends mesially to the lateral border of the rectus abdominis muscle, 1 cm. above the crural arch. Section of the muscle begins at the top and continues down to the subperitoneal adipose tissue. The peritoneum is separated, the iliac artery isolated and compressed and the pelvic ureter finally isolated. Two types of cases may present complications: (1) Cases in which the stone is engaged in the juxtavesical segment. Here it is necessary to isolate the ureter until the point where it crosses the vas in the male. A number of small veins may have to be cut. If the stone is not discovered at the moment of operation, the pelvis is explored with the index finger, combined palpation being performed with the surgeon's finger in the small pelvis and the assistant's in the rectum or the vagina. With strong light and well placed retractors, it is easy to isolate the stone, the assistant pushing it up by vagina or rectum. (2) Cases in which the ureter at the level of the stone is sheathed by an indurated mass. It is fortunate that this type is not common for it presents a great difficulty, especially if there is marked periureteritis. To prevent lacerating the large veins, one should operate close to the ureter, but there are cases in which the ureter may not be recognizable in the mass that surrounds and penetrates it; here, it is better to give up the idea of isolating it and to open the canal in the iliac or parietal segment, that is, in the free tract above the mass, and extract the calculus with small stone forceps. Operation should be reserved for stones of 2 cm. or more in diameter; for smaller ones, endoscopic maneuvers are preferable.

[COMPILER'S NOTE.—Ureterolithiasis may present various problems, but, as Rolando stated, in most instances when the stone is smaller than the physiologic lumen of the ureter, it may pass spontaneously or by

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23. Rolando, Silvio: Observations sur la lithiase urétérale, *J. d'urol.* 36:145 (Aug.) 1933.

cystoscopic maneuvers. In these cases it is desirable to recognize the value of an indwelling ureteral catheter in an effort to secure drainage, relieve infection and further dilate the walls of the ureter, thus assisting the passage of the urinary calculus and preserving renal function.]

*Physiology.*—Cusani<sup>24</sup> denuded of its adventitia a tract of ureter varying from 1 to 3 cm. in length, in dogs, with a view to getting a better understanding of the physiopathology of hydronephrosis. In nearly every one of his 10 experiments this gradually produced dilatation along the ureter above the tract denuded, which frequently continued up into the renal pelvis and finally, after a lapse of several months, into the calices and even into the renal parenchyma. In a late stage, the solid parts of the kidney tended to disappear progressively through atrophy; the glomeruli formed small cysts, with atrophy of their vascular loops, and the tubules were reduced to cords of epithelial cells or dilated segments which in some places appeared to be similar to true cystic dilatations. In cases like these, when obstruction is not the cause of the phenomena observed, it must be that the ectasia of the tubular apparatus of the kidney and its excretory duct, with all the other changes described, is the result of dystrophic disturbance of the wall comparable to what is recognized as the cause of polycystic kidney. This disturbance is evidently due to interruption of the nerve supply resulting from removal of the adventitia, and it is betrayed in a purely dynamic factor, since the abnormal dilatation evidently leads to marked disequilibrium of the entire hydraulics of the renopyelo-ureteral system, a disequilibrium which, as can readily be seen, may have an injurious effect on the walls of all the glomeruli and tubules. It is to this dynamic factor that Cusani wishes to draw attention as a means of explaining so many clinical disturbances which, although without characteristic signs in their early stages, may culminate in the picture of a renal colic. Recent observations of Blatt, Caporale, Cusani and others seem to demonstrate that peristalsis of the ureter and renal pelvis is regulated by neuroganglionic automotor centers situated in the adventitia of their walls, and that a lesion of these centers gives rise to pyelo-ureteral dilatation through paralysis and atony of the musculature. Such studies constitute a sound experimental basis for the dynamic theory as a means of unifying the physiopathology and pathogenesis of different forms of hydronephrosis. Even in hydronephrosis from calculosis, in addition to an obstructive action, there are grave lesions involving the muscular wall and pyelo-ureteral contractility; in other words, a primary mechanical factor has been supplemented later by a dynamic one. The atony in these cases is never primary but presupposes a profound lesion of the central,

24. Cusani, M.: Sulle alterazioni a tipo idronefrotiche nel rene consecutive alla simpaticectomia periureterale, *Ann. ital. di chir.* 11:1032 (Sept. 30) 1932.

peripheral and sympathetic neuromuscular system which may be the result of compression, stretching, inflammation or, as frequently occurs, of infection.

*Tumors.*—Snyder and Wood<sup>25</sup> reported a case of primary carcinoma of the ureter. The cardinal symptoms of pain and hematuria were present, but there was nothing in the history to distinguish the condition from other, more common urinary disturbances. Catheterization and pyelograms revealed an obstructing lesion low in the right ureter, which, coupled with the physical signs of a mass in the right lower abdominal quadrant, suggested ectopic kidney. They stated that, in view of the condition found at operation and at necropsy, it seemed probable that a successful result might have been expected if the patient had been seen earlier in the disease. Excision of the growth followed by nephrectomy, which was the treatment indicated, could not be carried out because of the poor condition of the patient. Death was primarily due to obstruction of the ureter, which in turn resulted in destruction of the kidney, with accompanying infection, ending in generalized loss of resistance and final overpowering infection. Snyder and Wood stated that ureteral tumors, like vesical tumors, as a rule metastasize late, making early operation with resection of the growth a worth-while objective.

Kirshbaum<sup>26</sup> reported 5 cases of true metastasis to one or both ureters, with the observations made at necropsy. The presence of tumor cells within lymph vessels of the ureteral wall was offered as the criterion of the true metastatic nature of the tumors. The ureter as a site of metastasis is very rare, only 11 cases having been reported in the literature exclusive of Kirshbaum's cases. True metastasis to the ureters should not be confused with invasion of the ureters by extension from such nearby organs as the uterus, prostate gland and urinary bladder when they are primarily involved. One of Kirshbaum's cases indicates that Hodgkin's lymphogranuloma behaves like a malignant tumor. In this case, nearly all the organs, including the ureters, were the site of granulomas which did not differ, in the way of spreading, from the 4 carcinomas.

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25. Snyder, W. H., Jr., and Wood, B. S.: *Primary Carcinoma of the Ureter*, J. Urol. **28**:577 (May) 1933.

26. Kirshbaum, J. D.: *Metastatic Tumors of the Ureters*, J. Urol. **30**:665 (Dec.) 1933.

(To be concluded)

## SYMMETRICAL TRAUMATIC FRACTURES OF THE CRANIUM; SYMMETRICAL FRAGMENTATION

COMMENTS ON THEIR MECHANISM

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During thirteen and a quarter years, one of us (E. R. L.) made or took part in 1,278 postmortem examinations of the bodies of persons who at the time of death had fresh or recent traumatic linear fractures of the cranium such as usually are produced by blunt force. Fractures due to bullets or other missiles are not included in this group, nor are cleancut sharply localized perforating wounds of the cranium due to cutting implements or weapons. Twenty-six of the 1,278 fractures were in persons not more than 1 year old; 45, in persons from 1 to 10 years of age and 29, in persons between the ages of 11 and 20 years. This proportion of fractures in adults, 1,178 of the 1,278, is about the same as Vance<sup>1</sup> found in 507 similar fractures, with 66 in persons in the first two decades of life. From time to time, publications have issued from different clinics and hospitals based on the clinical and anatomic observations on fractured skulls during certain periods.<sup>2</sup> It is interesting to find in examining such studies that the features of cranial fractures encountered a few decades ago are different from those now prevalent. In the large series analyzed by Vance,<sup>1</sup> as well as in those furnishing material for our study, long radiating fractures are numerous. A number of years ago, localized fractures with comminution and depression were relatively more common. This change is undoubtedly a result of the increase in accidents from motor vehicles.

During our postmortem examinations, the course of the fractures was carefully drawn on printed charts. As a routine measure the

From the Norman Bridge Pathological Laboratory of Rush Medical College.

1. Vance, B. M.: *Fracture of the Skull: Complications and Causes of Death; A Review of Five Hundred and Twelve Necropsies and of Sixty-One Cases Studied Clinically*, Arch. Surg. 14:1923 (May) 1927.

2. (a) Dwight, E. W.: *A Study of One Hundred and Sixty-Nine Autopsies in Which Fractures of the Skull Were Found*, M. & S. Rep. Boston City Hosp., 1894, p. 129. (b) Brun, H.: *Der Schädelverletzte und seine Schicksale*, Beitr. z. klin. Chir. 38:192, 1903.

diagrams thus made were compared with the fractures by a second, and often a third, person to confirm their accuracy. Tension was made to spread open the fractures, fragments being pulled apart slightly to determine the limits and connections of the fissures. In examining these sketches recently, it was found that some of the fractures were distributed equally on the right and left sides of the skull, or that fractures coursing in the sagittal midline had broken the cranium in lateral halves. The resulting symmetry of fractures and fragments is by no means perfect in the 80 selected from the 1,278 fractures because of such characteristics.<sup>3</sup> In a few, the symmetry is beautiful, but in most of the 80 there are some deviations or irregularities; however, there are not enough for their inclusion with the more perfect fractures to lessen their usefulness in this study.

A great deal of attention has been devoted to the way the skull breaks from external blunt violence.<sup>4</sup> Many of the investigations have been experimental. The desire to compare accepted views regarding the mechanism of linear skull fractures with the information available concerning the 80 fractures was both natural and irresistible. Experiments have failed to reproduce similar symmetrical fractures with any regularity. The symmetry or approach to symmetry in the 80 fractures suggested a greater likelihood of obtaining notions from them of how craniums break than from a study of the usual run of skull fractures from which they were selected. Almost one half of the 80 are ring-shaped fractures about the foramen magnum, mainly in the posterior fossa, or spread out so as to include the posterior fossa and also portions of the middle fossa and the vault.

We have not attempted to fix the time definitely when the casual relationship of the spine and the weight of the body and its extremities to ring fractures about the foramen magnum was first fully understood. New ideas are often announced independently from several sources and sometimes at intervals of many years before they are integrated and conventionalized. So far as French literature is concerned, there is some indication that the explanation by Berchon<sup>5</sup> in 1862 of a ring fracture of the base of the skull was novel. The

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3. Symmetrical fractures of the mandible, of other bones of the face and of the zygomatic arches have been omitted.

4. Two other articles on skull fractures based on some of this series of 1,278 fractures have been published: (a) Le Count, E. R., and Apfelbach, C. W.: *Pathologic Anatomy of Traumatic Fractures of Cranial Bones*, J. A. M. A. **74**: 501 (Feb. 21) 1920. (b) Apfelbach, C. W.: *Studies in Traumatic Fractures of the Cranial Bones*, Arch. Surg. **4**:434 (March) 1922.

5. Berchon, E.: *Fracture communicative du frontal avec enfoncement des fragments et irradiations nombreuses et étendues*, Bull. Soc. anat. de Paris, series 2, **7**:80, 1862.

fracture occurred in a man who fell into the hold of a ship that was under construction (fig. 1). Berchon made a complete break from traditional explanations of fracture by contrecoup and said that the basilar fracture was direct and produced by the shock of the cervical vertebrae charged with all the weight of the body. Trélat, in discussing Berchon's report, frankly said that this was a new way of accounting for such fractures. Previous to this time, Trélat had made two noteworthy contributions to the subject of skull fractures.<sup>6</sup> He also had described a ring fracture in the posterior fossa in a report on a necropsy which was added to a clinical account by Tarnier.<sup>7</sup> In this case, a man, aged 50, had fallen headlong out of a window onto a paved court and died at once. Interest in his injuries apparently

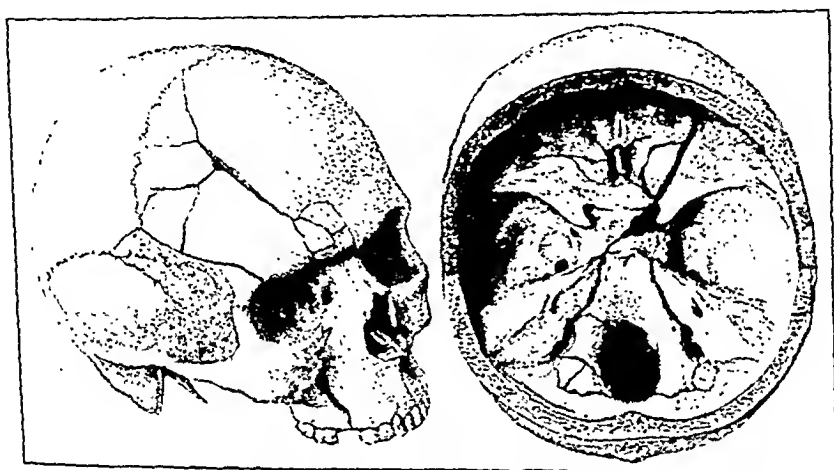


Fig. 1.—The ring fracture reported by Berchon in 1862. (From Berchon: *Bull. Soc. Anat.*, series 2, 7:80, 1862.)

was mainly in a torn articular cartilage of the left knee, for Broca, Fano, Verneuil and Bourcy discussed Tarnier's presentation without mentioning the cranial fracture. Although Trélat said, in describing the fracture, "Il résulte de la multiplicité de ces lésions et de la direction des lignes suivies par elles, que la partie centrale de la base du crâne formait une sorte d'anneau irrégulier complètement indépendant du rest du crâne et reste seul en connection avec la colonne vertébrale," he said nothing as to the actual method of its production. But when Trélat heard Berchon's report seven years later, he recalled

6. Trélat, U.: (a) *Mémoire pour les prix de l'Internat*, 1852; (b) *Des conditions de résistance du crâne*, *Bull. Soc. anat. de Paris*, series 1, 30:121, 1855.

7. Tarnier: *Décollement traumatique d'un cartilage; fracture du crâne*, *Bull. Soc. anat. de Paris*, series 1, 30:193, 1855.

the fractured skull in Tarnier's patient and supplied an illustration to accompany that of the ring fracture described by Berchon (fig. 2). E. Simon, secretary for the society when these announcements and discussions took place, paid high tribute to Berchon in his review of the work for 1862, thanked him for the society and said that they were honored by having such an important matter presented to them.<sup>8</sup>

This account is remarkable, because Denucé,<sup>9</sup> in discussing the paper by Trélat in 1855, criticized him severely for failure to emphasize the influence of the spine. Among other statements by Denucé is this:

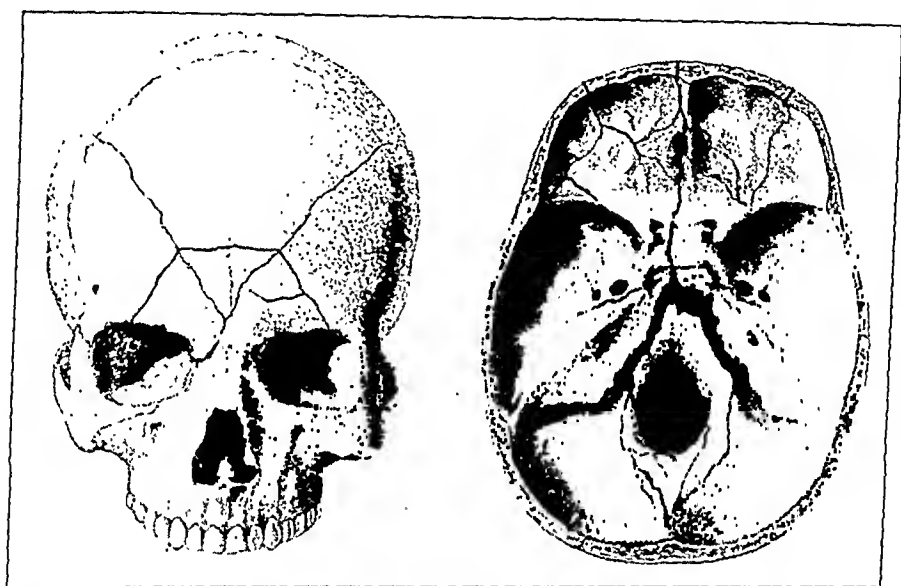


Fig. 2.—The ring fracture reported by Trélat in 1855. (From Trélat: *Bull. Soc. Anat.*, series 1, 30:121, 1855.)

Enfin un dernier reproche que je ferai à M. Trélat, c'est d'avoir négligé complètement les conditions de résistance que peut offrir le crâne lorsque le choc vient de bas en haut, et dans tous les cas, l'action que doit exercer le poids du corps par l'intermédiaire de la colonne vertébrale sur la base du crâne, alors même, comme cela se présente dans beaucoup de chutes, que le choc principal atteint la voûte.

It is altogether likely that when Berchon's presentation was made, Trélat was fully aware of the action of the spine and the weight of the trunk, but had not connected them with ring fractures about the foramen magnum. It is well to recall that when these events occurred almost a century ago, controversy was still active regarding isolated fractures distant from the place injured: *contrecoup* fractures, as they were

8. Simon, E.: *Bull. Soc. anat. de Paris*, series 2, 7:534, 1862.

9. Denucé, in discussion on Trélat,<sup>6b</sup> p. 132.

called. The polemic, beginning with the time of Hippocrates,<sup>10</sup> had its first period of merely differences of opinion concluded by the efforts of the French Academy of Surgery to secure a satisfactory answer to the problems of such fractures by offering prizes in 1760, 1765 and 1768.<sup>11</sup> Among the awards was one to Saucerotte for his vibration theory. Briefly stated, this predicated a disrupting ebullition of vibrations where they came together at the opposite pole after traveling around the skull in various meridians from the place struck.

During the second period, which ended with the publication of studies by Aran,<sup>12</sup> the theory of Saucerotte dominated, and these fractures received relatively little attention. It is of interest that Aran called them independent fractures. Since his announcement of the paths taken when fractures radiate from the vault to the base of the skull, there have been no definite periods of discussion. Schroen,<sup>13</sup> referring probably to the measurements of cranial elasticity by Bruns,<sup>14</sup> said:

Deutschen Forschern gelang es, die rechte Fährte zu finden; schon schien es als ob das Ziel diesmal in Wirklichkeit erreicht würde, schon reifte die Frucht der suchenden Hand entgegen, als abermals von Frankreich eine neue fascinierende Theorie die deutschen Arbeiten zum Stocken brachte, es war die Félizet'schen Hypothese,<sup>15</sup> die man im Gegensatze zu der ersten physicalischen französischen Theorie die "anatomische" nennen könnte.

This anatomic period of Aran and Félizet, with many embellishments from physics, still prevails. But the Saucerotte vibration theory died out slowly, and for many years any observation of an independent fracture of the cranial base was likely to find its way into literature. Alone or associated with other fractures, and regardless of their loca-

10. Many accounts of the development of the present knowledge of the mechanism of these independent cranial fractures have been written. The following are perhaps the most complete: (a) Friedberg, H.: *Klinische und forensische Beiträge zu der Lehre von den Kopfverletzungen*, Virchows Arch. f. path. Anat. **22**: 39, 1861. (b) Dulles, C. W.: *The Mechanism of Indirect Fractures of the Skull*, Tr. Coll. Phys., Philadelphia **8**:273, 1886. (c) Schroen, F. W. C. A.: *Historisches und Theoretisches zu der Lehre von den Schädelbrüchen, speziell den sog. Gegenbrüchen*, Inaug. Dissert., Würzburg, C. J. Becker, 1902.

11. *Mémoire sur le sujet proposé pour le prix de l'académie royale de chirurgie*, Paris, 1778, vol. 4.

12. Aran, F. A.: *Recherches sur les fractures de la base du crâne*, Arch. gén. de méd., series 4. **6**:180 and 309, 1844.

13. Schroen,<sup>10c</sup> p. 4.

14. von Bruns, V.: *Handbuch der praktischen Chirurgie*, Tübingen, H. Laupp, 1854, p. 203.

15. Félizet, G. M.: *Recherches anatomiques et expérimentales sur les fractures du crâne*, Paris, A. Delahage, 1873.



tion, they are uncommon. Deroubaix,<sup>10</sup> however, said that he often saw them in his own postmortem work and regretted his failure to keep accurate records of them. In discussing fractures of the base of the skull in relation to incidence, most writers, probably influenced by the work of Aran,<sup>12</sup> have been content to state the number of fractures radiating into this or that fossa from the vault, and how many as well as which fossae were involved, when the fracture, or fractures of both the base and the vault, coursed through more than one fossa. But few writers have recorded how many fractures in their series were strictly limited to the base of the skull. Schwartz<sup>17</sup> found 7 among the 115 cases which he analyzed; Walton,<sup>18</sup> 7 among 50, and Phelps,<sup>19</sup> in three contributions, mentioned 4 in 45, 17 in 126 and 15 in 312, respectively.

The infrequency of fractures confined to the base of the skull has not been the sole reason for the many reports concerning them. Advantage has been taken of the opportunity offered by such fractures to repeat refutation of their origin by contrecoup vibration. In 1842, Guthrie<sup>20</sup> said:

The late Mr. Earle supposed that a fracture of the base of the cranium depended on the occiput being forcibly impelled against the atlas. Sir Charles Bell has maintained the same opinion, and given a scientific account of the manner in which the mischief takes place. It appears to me that this accident principally depends on the superincumbent weight of the body pressing on the unsupported flat, and thin base of the skull, and is but little connected with the unyielding nature of the spine; for it occurs to as great an extent in consequence of falls from a short distance without any impetus, as from falls from a great height.

A number of years before, the opinions of Mr. Earle were also stated by Brodie,<sup>21</sup> who wrote, regarding contrecoup fracture:

It has been observed to me, however, by Mr. Earle, that he has not known a fracture of this kind to take place, except where the blow seems to have operated

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16. Deroubaix: De la lésion de certain nerfs, considérée comme moyen de diagnostic des fractures de la base du crâne, Bull. Acad. roy. de méd. de Belgique, series 4, 4:740, 1890.

17. Schwartz, A.: Zur Statistic der Fracturen der Schädelbasis, Inaug. Dissert., Dorpat, 1872.

18. Walton, G. L.: Fracture of the Base of the Skull, Ann. Surg. 40:654, 1904.

19. Phelps, C.: (a) A Clinico-Pathological Study of the Injuries of the Head, New York M. J. 57:29, 1893; (b) Traumatic Injuries of the Brain and Its Membranes, New York, D. Appleton, & Company, 1897; (c) Analytical and Statistical Review of One Thousand Cases of Head Injury, Ann. Surg. 49:449, 1909.

20. Guthrie, G. J.: On Injuries of the Head Affecting the Brain, London, J. Churchill, 1847, p. 65.

21. Brodie, B. C.: Pathological and Surgical Observations Relating to Injuries of the Brain, Med.-Chir. Tr., London 14:325, 1828.

in such a manner as to impel the occiput forcibly against the atlas, the line of fracture passing through the former bone where it rests on the latter.

These comments are not concerned directly with ring fractures about the foramen magnum. Ring fractures acquired whatever they now possess of entity and comprehension only gradually and during the years when, as already stated, case reports of all sorts of independent fractures of the base of the skull were customary.

In some skulls, basal fractures are the only ones present. For these, we believe that the term solitary basal fracture is most suitable. We prefer to restrict the name independent to fractures associated, but not continuous, with the main fractures located at, and radiating from, the site of violence. Many writers call them indirect, whether they are solitary or not. By many, the terms contrecoup and indirect have been used synonymously; even in recent years, these fractures have occasionally been labeled contrecoup.

Robert, in 1843,<sup>22</sup> reported fractured posterior clinoid processes associated with a fracture across the right petrous bone, the skull bones being otherwise intact. Robert thought that the fracture in the petrous bone was contrecoup, but Aran said regarding it:

Nous ne voulons pas disputer sur ce fait, nous l'acceptons tel qu'il est; mais nous ne pouvons voir là une fracture par contre-coup. Qu'importe, en effet, que la puissance exerce son action d'une manière immédiate sur la base du crâne ou qu'elle y arrive par l'intermédiaire de la colonne vertébrale?

The body was that of a mason who had fallen 12 meters, striking feet first. Announcements of similar fractures were so few at this time that von Bruns,<sup>23</sup> a decade later, mentioned only one other,<sup>24</sup> with that reported by Robert, as examples of basal fractures due to transmission of violence by the spine. The report by Marmy, concerned fractures also due to alighting feet first; in the cranium the ethmoid cribriform plate was broken by a solitary fracture. Another report of such fractures of the base by Marmy, which Bruns should have included.<sup>25</sup> dealt with

22. Robert: *L'expérience*, J. de méd. et chir. pract., Nov., 1843; as cited by Aran, and many others. These fractures are illustrated by Victor von Bruns in *Chirurgischer Atlas. Bildliche Darstellung der chirurgischen Krankheiten und der zu ihrer Heilung erforderlichen Instrumente, Bandagen und Operationen*, Tübingen, H. Laupp, 1853, fig. 22, plate IV.

23. von Bruns,<sup>14</sup> p. 281.

24. Marmy: *Fractures multiples (du calcanéum, du crâne, et du radius)*, Bull. Soc. anat. de Paris, series 1, 23:258, 1848.

25. Marmy: *Fractures du crâne et déchirure du poumon et du foie. Epanchement du sang dans l'abdomen; fracture du poignet*, Bull. Soc. anat. de Paris, series 1, 23:193, 1848. Both reports by Marmy are cited by Denonvilliers and Gosselin (*Compendium de chirurgie pratique*, Paris, 1851, p. 580) as examples of fractures caused by blows of the spine from below, as they were subsequently cited by E. von Bergmann (*Die Lehre von den Kopfverletzungen*, in *Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1880, pt. 30, p. 208).

fractures in the right petrous bone and body of the sphenoid in a man who fell from a second story window and alighted on his hands and knees. Bruns<sup>26</sup> emphasized the manner in which the skull is compressed vertically by the weight of the oncoming trunk after the head is arrested, but he did not mention ring fractures.

If it is true, as Guthrie said, that Bell understood "how the mischief takes place," he may indeed have been the first to observe a ring fracture of the base of the skull and at the same time the first to comprehend its mechanism. He described a fracture<sup>27</sup> that "began by the side of the petrous bone of one side, and extended around the occipital bone behind the foramen magnum to the petrous portion of the temporal bone of the opposite side." It was caused by a bucket which fell 50 feet and hit the back of the head of a man in a tunnel. As will be shown presently, this is an important observation. Bell went on to say that the blow was received "on the strongest part of the skull, in the convexity of the occipital bone; the fissure was in the weakest part." The fracture was an incomplete ring with the gap in front, and belongs to the type we are discussing. But it is not altogether evident that Bell was fully aware that resistance from below assisted in producing the fracture, for he concluded with: "It was a pure instance of counterfissure."

Forgues<sup>28</sup> mentioned symmetrical fractures described by Couderc,<sup>29</sup> one on each side from the lambdoid suture to the jugular foramens. Such fractures are portions of a ring.

In 1858, Hewett<sup>30</sup> described a similar incomplete ring fracture due to a fall of about 20 feet (6 meters); the scalp wound was on the right side of the vertex behind. In the body of a man 32 years old, who fell off a scaffolding, Bryant<sup>31</sup> found that "the weight of the body, as conveyed through the spine, had completely driven the spinal column into the skull, the base for about one inch round the foramen magnum being detached and pressed inwards upon the brain; this was much lacerated and contused from the pressure of the displaced bone; fissures radiated upwards from this spot." The cranial vault was uninjured. Accompanying fracture of both articular processes of the epistropheus,

26. Bruns,<sup>14</sup> p. 285.

27. Bell, C.: *Surgical Observations*, London, Longmans, 1816, p. 467.

28. Forgues, L. D.: *Mécanisme des fractures du crâne*, Thèse de Strasbourg, 1869, p. 30.

29. Couderc, J. A.: *Sur les fractures du crâne*, Thèse de Paris, 1850.

30. Hewett, P.: *Lectures on the Anatomy, Injuries and Diseases of the Head*, M. Times & Gaz. 16:27, 1858.

31. Bryant, T.: *The Injuries and Diseases of the Nervous System*, Guy's Hosp. Rep. 20:59, 1859; case 36.

Gurlt<sup>32</sup> found a piece broken from the rim of the foramen magnum. The injuries were in the body of a man 24 years old, who fell head first from a wagon and struck on the crown of his head. Discussion of this fracture by von Bergmann a few years later<sup>33</sup> leaves the impression that the piece broken off was from considerable of the circumference of the margin of the foramen. The large ring fracture described by Chauvel<sup>34</sup> was elliptic. Its posterior end was formed by the foramen magnum. Branches beginning on each side behind the occipital condyles forked symmetrically, with short arms ending in the lower occipital fossae and long arms extending forward through each petrous bone and each greater wing of the sphenoid to meet just behind the crista galli. Chauvel's thesis contained no illustrations, but Chipault and Braquehay<sup>35</sup> showed the path of this ring in a diagram of the outside of the base of the skull. The injuries were due to a fall of 2.5 meters so as to alight on the head; the scalp wound was in the right parietal region, and the vault was not broken. Both Félizet<sup>36</sup> and Forgues<sup>37</sup> dealt with Chauvel's fracture at length. Inspired by his examination of this ring fracture, Chauvel attempted to make a similar fracture experimentally. In 1 skull he obtained rather symmetrical fractures, 3 cm. long on one side and 5 cm. long on the other, running back from each jugular foramen into the inferior occipital fossae. The body was that of a hunch-backed man, 73 years old, with the first 6 vertebrae ankylosed. Chipault and Braquehay<sup>38</sup> also illustrated the injuries in this skull.

Some indication of the attention these ring fractures received at this time is evident in the circumstantial description given of one of them by Hutchinson.<sup>39</sup> One of the two fine illustrations accompanying his report was reproduced by von Bergmann.<sup>40</sup> Hutchinson said, "it is very unusual in practice to find the line of fracture symmetrical, probably because in but few instances is the direction of the violence exactly

32. Gurlt, E.: *Handbuch der Lehre von den Knochenbrüchen*, Hamm, G. Grote, 1862, p. 35.

33. von Bergmann: *Verletzungen und chirurgische Krankheiten des Kopfes*, in Pitha and Billroth: *Handbuch der allgemeinen und speciellen Chirurgie*, Stuttgart, Ferdinand Enke, 1873, vol. 3, p. 129.

34. Chauvel, F.: *Essai sur les fractures du crâne*, Thèse de Paris, 1864, p. 66.

35. Chipault, A., and Braquehay, J.: *Etudes graphiques sur les fractures indirectes de la base du crâne (définition et mécanisme)*, *Arch. gén. de méd.*, series 8, 4:279, 394 and 665, 1895, fig. 22, p. 292.

36. Félizet,<sup>15</sup> p. 145.

37. Forgues,<sup>25</sup> p. 12.

38. Chipault and Braquehay,<sup>35</sup> fig. 23, p. 292.

39. Hutchinson, J.: *Circular Fracture of the Base of the Skull with Features of Unusual Interest*, *Tr. Path. Soc. London* 17:254, 1866.

40. von Bergmann,<sup>33</sup> p. 130.

vertical." The basilar process, occipital condyles, body of the sphenoid and inner halves of the petrous bones made "one nearly circular fragment." A fissure from the ring ran up in the vault from the right middle fossa. The fracture was due to a headlong fall, and Hutchinson understood the part played by the impact of the spine and the weight of the trunk in its production. Schwartz<sup>41</sup> failed to state where he found the elliptic fracture of the base which he said encircled the foramen magnum, sella turcica and crista galli. The particulars of its course are similar to those of the elliptic ring fracture described by Chauvel.<sup>34</sup> The review by Schwartz comprised fractures in 115 skulls; 14 from the Dörpat collection, 25 from Obuchow and 75 from the literature. Details of the course of the fractures were meager in about one half of the 115 cases. Only 7 were limited to the base, and only 1 was a ring fracture.

Félizet<sup>42</sup> broke out a large circular piece from the base of the skull experimentally without fracturing the vault. It was nearly all ventral to the foramen magnum and included the sella and a large part of each petrous bone. He did this by hitting the padded vertex with a large hammer. The support for the base was patterned after the spine. The following is an account by Bennett<sup>43</sup> of the injuries he found in the cranium and spine of a man hit on the head by a weight which fell 34 feet (10 meters).

. . . having been checked in the fall at a distance of nine feet above the ground. . . . There was an ordinary depressed fracture of the parietal bone, and a fracture by radiation was marked by a fissure extending from the depression to the orbital plate of the sphenoid bone, and passing into both optic foramina. . . . The base of the cranium was fractured over each occipital condyle, and an oblique fracture passed outward from the foramen magnum to end in the petrosal sinus. The transverse process of the first cervical vertebra was detached, the spine had been driven upward and was actually impacted into the cavity of the cranium. The posterior clinoid processes were also detached.

The scalp wound was in the left parietal region. Symmetrical fractures from each jugular foramen to about 1 cm. behind the occipital condyles, associated with detached posterior clinoid processes, fracture of the body of the sphenoid bone and loosened sutures between the occipital and the temporal and parietal bones on the right side, were reported by Magon.<sup>44</sup> They were in the head of a man 43 years old who fell backward and head first from a ladder.

41. Schwartz,<sup>17</sup> p. 19, case 4.

42. Félizet,<sup>15</sup> p. 146, plate 13.

43. Bennett: Fractures of the Cranium, *Brit. M. J.* 1:326, 1875.

44. Magon, E.: Fractures multiples du crâne, *Bull. Soc. anat. de Paris*, series 3, 10:247, 1875.

Symmetrical fractures from each side of the foramen magnum through the thin bone of the inferior occipital fossae, then forward to each jugular foramen, formed the rear of a ring fracture described by Petit.<sup>45</sup> It was completed in front by petrobasilar diastasis. It followed a fall so as to alight on the head. Von Bergmann<sup>46</sup> described and illustrated an asymmetrical ring fracture with considerable comminution in the back of the base of the skull. He observed it when he was at Dorpat, where so many studies of cranial fractures were subsequently made (Schwartz, 1872; Hermann, 1881; von Wahl, 1883; Greiffenhagen, 1887, von Knorre, 1890, and others). It was produced by a fall from a great height. He found accounts of only 5 other ring fractures at that time. Laurand<sup>47</sup> found complete detachment of each occipital condyle by fractures surrounding them closely. A branch ran out to the groove for the lateral sinus from the left small pericondylar ring, and from the right ring, a branch ran to the mastoid. The right petrobasilar suture was torn open, and through the middle fossae and body of the sphenoid bone a transverse fracture coursed. These injuries were in the cranium of a coachman who fell head first to the pavement while trying to recover the reins; he died two days later.

Part of an incomplete ring fracture in an illustration by Schranz<sup>48</sup> includes a transverse fracture of the clivus; it was made experimentally by indirect violence to imitate force transmitted by the spine. Hermann<sup>49</sup> found 61 reports of skull fractures in the medical literature published subsequent to the review by Schwartz ten years previously. These fractures, with 8 broken skulls he found in the Dorpat collection, 5 furnished him by Körber and another by Luken, together with the fractures he made experimentally in 17 heads, formed the basis for his study. He divided basilar fractures into transverse, lengthwise, diagonal, ring and nondescript. In his 92 cases, there was no ring fracture. One of the 2 incomplete ring fractures in the illustrations accompanying von Wahl's article<sup>50</sup> was found in Lukin's collection at Kronstadt. The fracture was caused by a fall head first on a stone floor, and was incomplete

45. Petit, C. H.: Fracture de la colonne vertébrale; fracture indirecte de la base du crâne; fracture incomplète de la première pièce du sternum, *Bull. Soc. anat. de Paris*, series 3, 10:62, 1875.

46. Von Bergmann,<sup>33</sup> p. 129, fig. 24.

47. Laurand, G.: Fracture du crâne, probablement par contre-coup; rupture de l'artère meningée moyenne, *Bull. Soc. anat. de Paris*, series 4, 4:721, 1879.

48. Schranz, J.: Untersuchungen über die Entstehung von Schädelbrüchen, *Med. Jahrb., Wien*, 1881, p. 291, plate XII.

49. Hermann, N.: Experimentelle und casuistische Studien über Fracturen der Schädelbasis, *Inaug. Dissert., Dorpat*, 1881.

50. von Wahl, E.: Ueber Fracturen der Schädelbasis, *Samml. klin. Vortr.*, 1883, no. 228 (*Chir. no. 73*), p. 1945; figs. 18 and 19, p. 1969.

behind. The other fracture, incomplete in front, was in a skull in the collection of the surgical clinic in Dorpat. How this skull was broken is not stated. The fractures in each skull belong to the small ring variety, and from each ring other fractures radiated.

One ring fracture is described and illustrated in the first of the two famous monographs by Messerer.<sup>51</sup> Another he demonstrated during an address at Munich.<sup>52</sup> Both were made experimentally and are reproduced here to illustrate the difference between them and the ring fractures commonly produced by human casualties. The first (fig. 3) was made by sawing off the skull cap and compressing the lower half of the skull with hydrostatic pressure in a Werder machine which

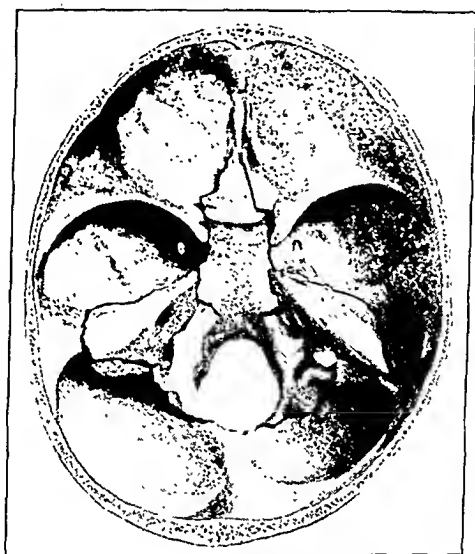


Fig. 3.—A ring fracture produced by Messerer. The calvarium was removed, and the base compressed in a Werder machine. (From Messerer: *Ueber Elasticität und Festigkeit der menschlichen Knochen*, Stuttgart, 1880, fig. 1, plate VII.)

recorded the force used. Messerer did not state how the second fracture (fig. 4) was produced. It is not illustrated or described in his monographs. A third ring fracture<sup>53</sup> was made by dropping a weight on top of a head still normally attached to the body. From the place hit, a fracture ran squarely across the vault into the right middle fossa, ending in the right carotid foramen. Around the foramen magnum there was a ring fracture enclosing the clivus, the left petrous bone

51. Messerer, O.: (a) *Ueber Elasticität und Festigkeit der menschlichen Knochen*, Stuttgart, J. G. Cotta, 1880; (b) *Experimentelle Untersuchungen über Schädelbrüche*, Munich, M. Rieger, 1884.

52. Messerer, O.: *Ueber die gerichtlich-medizinische Bedeutung verschiedener Knochenbrüche-Formen*, Friedreich's Bl. f. gerichtl. Med. 36:81, 1885.

53. Messerer,<sup>51b</sup> p. 12, experiment 66.

and both anonymous processes of the rim of the foramen magnum. Messerer did not state its course on the right side; it probably followed the petrobasilar suture. In his experiment 68,<sup>54</sup> he also broke the skull across with isolated fractures of each anonymous process and a separate fracture lengthwise in the clivus. This, Messerer labeled ring fracture. There are no illustrations of the ring fractures in experiments 66 and 68. In 2 other skulls, independent fractures of the base were produced, which Messerer regarded as suggestions of ring fractures.

Dulles summarized the particulars of the fractures in 119 craniums. In his final illustration,<sup>55</sup> the course of 100 fractures is represented in the customary single diagram of the inside of the base of the cranium. One cannot decide whether in the great number of lines in this composite picture there are included many representing ring fractures about the

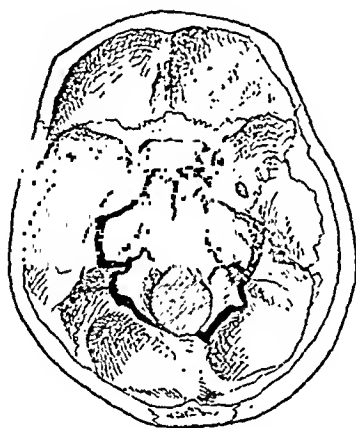


Fig. 4.—A ring fracture Messerer showed at Munich in 1885. Judging from its description, it was produced by a falling weight. (Messerer: *Freidrich's Bl. f. gerichtl. med.* 63:81, 1885.)

foramen magnum. In examining the literature, as he must have done to assemble so many fractures, Dulles undoubtedly saw accounts of a number. Perhaps the best indication of the degree of his interest in these ring fractures is in this statement: <sup>56</sup>

Finally I have been struck by the fact that certain peculiar fractures of the base seem to have been due to support of a segment of the occipital bone furnished by the inclination upward and outward of the articular surfaces of the atlas which embrace the condyles of the occipital bone and restrain it from rupture to such an extent that a fracture will pass on both sides of the protected region rather than through it. This form of fracture I illustrate by a beautiful specimen taken from the Mütter Museum.

54. Messerer,<sup>51b</sup> p. 12.

55. Dulles,<sup>10b</sup> plate XXVII.

56. Dulles,<sup>10b</sup> p. 308.



But to which illustration he referred is not evident.<sup>57</sup> In one figure<sup>58</sup> an incomplete ring fracture is shown about the cribriform plate, and presumably this is alluded to in his statement: "One shows a ring fracture, in addition to . . ." At this time, Dulles' interest was mainly in the experiments by Messerer and others published shortly before. A number of years later, he was more explicit about ring fractures. He said:<sup>59</sup> . . .

An interesting form of violence, applied to the skull is that due to falls on the feet, where the momentum of the body is suddenly arrested by the resistance of the earth. In such a case a ring of bone surrounding the condyles may be driven into the skull.

Körber,<sup>60</sup> in medicolegal work at Dorpat, found 2 ring fractures, both quite symmetrical, about the foramen magnum. One was inside the other in the head of a man struck with the falling wing of a windmill. The outer ring was about as large as it could be in its posterior half and also remained confined to what is usually included in the bottom half of the cranium. It surrounded each petrous bone and the dorsal part of the body of the sphenoid bone. The inner ring included the occipital condyles and pars basilaris of the occipital bone. Also symmetrical and quite like this inner ring was another fracture Körber found in the body of a boy 10 years old, whose head was crushed against the spine by machinery. It was similar to ring fracture 25 (fig. 6) in our series but much more symmetrical. Körber's ring crossed the middle of the internal median crest in the posterior fossa. From all 3 ring fractures described by Körber, other fractures radiated.

In the article by Anna Heer<sup>61</sup> a small ring fracture is illustrated which began back of each occipital condyle with its front across the clivus from the apex of one petrous bone to the other. Passing out from each side of the ring were symmetrical fractures that broke the petrous bones across in their outer halves and ran forward toward the sphenoid fissures so as almost to complete a second ring in front of the first. From this second unfinished ring, a fracture radiated up in the vault on the right side, parallel with the coronal, and almost to the sagittal,

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57. The course of each of the 119 fractures was shown by drawings he presented to the College of Physicians in Philadelphia. Such separate treatment was not carried out in his published article.

58. Dulles,<sup>10b</sup> plate III and p. 314.

59. Dulles: Remarks on Fractures of the Skull, *M. News* 68:81, 1895.

60. Körber, B.: Gerichtsärztliche Studien über Schädelfracturen nach Einwirkung stumpfer Gewalten, *Deutsche Ztschr. f. Chir.* 29:544, 1889, plates 10, 10A and 10B, 11, 13A and 13B.

61. Heer, A.: Ueber Schädelbasisbrüche, *Beitr. z. klin. Chir.* 9:1, 1892, fig. 7, plate II.

suture. A fall of from 9 to 10 meters caused the injuries. The scalp wound was over the right parietal bone close to the vertex.

Chipault and Braquehay<sup>62</sup> referred to a ring fracture presented by Valude to the anatomic society of Paris and illustrated it with a diagram of the outside of the base of the skull. It began behind each occipital condyle, and on the right side ran along the petrobasilar suture, then obliquely across the front end of the basilar plate to the apex of the left petrous bone; from here it ran through the left carotid canal to the front of the left petrous bone, and across this bone to the left jugular foramen, then behind the left condyle. From its inner side, branches sprang so that each occipital condyle was completely and closely encircled by a small ring within the larger one. Chipault and Braquehay did not give any reference as to where Valude's observations were published, nor did they tell how the injury occurred.

Van Nes portrayed a partial ring<sup>63</sup> formed by two symmetrical fractures, one on each side of the clivus. They ran from the carotid canals as far back as the outermost part of the foramen magnum, ending in the inferior occipital fossae. They were convex outwardly and would have been parts of a small ring, had it been complete. They were in the skull of a man who jumped through a window, alighting on his feet.

Symmetrical fractures in 4 skulls are described by Phelps, but there are no diagrams or other illustrations. One<sup>64</sup> fracture was due to a fall on the sidewalk. "The whole central portion of the occipital bone from the foramen magnum upward, and posterior portion of both parietal and right temporal bones, forming an irregular circle from two inches and a half to three inches in diameter, were broken into large fragments." Among the 80 fractures in our illustrations, there is none like this. In the other 3 skulls<sup>65</sup> fractures ran on each side of the foramen magnum from the occipital fossae, but failed to form rings. Phelps did not learn how these last 3 fractures were produced. A ring fracture which surrounded all the occipital and right petrous bones with its front end across the sella turcica was produced experimentally by Quenu and Tesson.<sup>66</sup> The dead body was thrown violently backward so that the occiput struck.

62. Chipault and Braquehay,<sup>35</sup> p. 292, fig. 19.

63. van Nes: Ueber Schädelbasisbrüche, *Deutsche Ztschr. f. Chir.* 44:593, 1897, fig. 2.

64. Phelps,<sup>19b</sup> case 7, p. 397.

65. Phelps,<sup>19b</sup> case 87, p. 446; case 88, p. 447; case 92, p. 449.

66. Quenu, E., and Tesson, R.: Des fractures postéro-antérieures para-médianes de la base du crâne, *Rev. de chir., Paris* 23:577, 1901. "Pièce no. 4."

In the English translation of the "Handbuch der praktischen Chirurgie,"<sup>67</sup> a small ring fracture is shown, with its front across the clivus and a fracture radiating from its left side through all of the base in front of the ring and then "extending to the frontal bone." Its course in the calvarium is not stated or illustrated. How it happened is not related. The patient died in von Bergmann's clinic.

Bohl's<sup>68</sup> references to ring fractures are chiefly confined to repeating statements by Körber about bending fractures of the base, that they are complete or incomplete rings made by compressing the sides, the front or back of the skull against the spine. Barnick's theme<sup>69</sup> was traumatic intralabyrinthine hemorrhage with basilar fractures. One of his 4 cases dealt with bilateral comminution in the posterior fossa with fractures leading out from each side of the rim of the foramen magnum, suggestions of rings and a somewhat symmetrical arrangement. They resulted from a fall of 3 meters. The superficial injuries were in the back of the scalp and of the right elbow. Stierlin<sup>70</sup> found at a postmortem examination what he regarded as calluses on each side of the foramen magnum and attributed them to a fall from a load of hay seven and a half weeks previously; a clinical diagnosis of ring fracture had been made, presumably from symptoms of injury to the ninth and twelfth cranial nerves.<sup>71</sup> There were other fractures in the base sagittally directed.

Graf's review<sup>72</sup> of 90 basal fractures is mainly clinical. There were 28 deaths and only 11 necropsies. Only 1 ring fracture is mentioned. Its course is described as close to nearly all the rim of the

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67. von Bergmann, Ernst; von Bruns, P., and von Mikulicz, J.: *A System of Practical Surgery*, translated and edited by William T. Bull and Walton Martin, Philadelphia, Lea Bros. & Co., 1904, p. 77, fig. 18.

68. Bohl, E.: In Sachen der Schädelbrüche, *Deutsche Ztschr. f. klin. Chir.* **43**:537, 1896.

69. Barnick: Brüche des Schädelgrundes, *Arch. f. Ohrenh.* **42**:22, 1897.

70. Stierlin, R.: Schädelbasisfraktur mit Lähmungen im Gebiete des X und XII Hirnnerven, *Arch. f. klin. Chir.* **61**:130, 1900.

71. In this connection see: Deroubaix,<sup>16</sup> Spiller, W. G.: A Physiological, Anatomical and Pathological Study of the Glossopharyngeal and Vagus Nerves in a Case of Fracture of the Base of the Skull, *M. Bull. Univ. Pennsylvania* **16**:13, 1903. Siebenmann, F.: Eine gleichzeitige Lähmung der Vagus-Accessorius-Glossopharyngeusgruppe als Folge von Schädelbruch, von Erhängungsversuch und von Sinusthrombose, *Ztschr. f. Ohrenh.* **65**:114, 1912. Lüken, E. A.: Ein-und gleichzeitige Vagus und Accessoriusläsion und vollkommene Taubheit nach Schädelbasisfraktur, *Arch. f. klin. Chir.* **104**:1000, 1914. Ulrich, K.: (a) Ueber Vagus, -Facialis, -und Acusticus-Verletzungen: Ein Beitrag zur Lehre von den Gehirnnerven-Läsionen bei Schädelbasisbrüchen, *Schweiz. med. Wchnschr.* **3**:545, 1922; (b) Verletzungen des Gehörorgans bei Schädelbasisfrakturen, *Acta oto-laryng.*, 1926, supp. 6.

72. Graf: *Deutsche Ztschr. f. Chir.* **68**:464, 1903, case 9.

foramen magnum, except where it ran out in the tabular part of the occipital bone. It was caused by a fall of 2 meters so as to alight on the head, and there was a small scalp wound above the occipital boss. Brun has 1 ring fracture in his long account of 470 skull fractures seen in the surgical clinic at Zurich from 1881 to 1901. There were 165 deaths. The ring fracture that he described and illustrated<sup>73</sup> was fairly large, through the middle of each petrous bone, the body of the sphenoid bone in front and close to the foramen magnum behind, being almost symmetrical with a fissure behind from the ring to the vault. It was due to a fall from a roof. The external injuries are not mentioned.

Among the diagrams in the article by Poulain,<sup>74</sup> 2 fractures are outlined which he included among transverse fractures. The first is credited to Jacob; the second to Borden, both without reference. These fractures cross the midline in or near the sella turcica and course so far along or within the front of the petrous bones that they may be regarded as the ventral halves of large ring fractures. A third fracture, also from Borden, was composed of three fourths of a large ring, incomplete from the right jugular foramen to the sella. There is no account by Poulain as to how these fractures were sustained.

The ring fracture encountered by Sharpe<sup>75</sup> was asymmetrical and accompanied by fractures of the pars basilaris, and by others radiating up in the vault. The injury was due to an aeroplane accident. A tub or vat falling on the head produced the large ring fracture illustrated by Reuter.<sup>76</sup> His figure is one of the relatively few representing the course of a fracture in the outside of the base of the skull. Vance<sup>1</sup> recognized two forms of skull fractures: linear and composite. Among those in the vault are also depressed fractures. He also grouped them as to location. He mentioned ring fractures in the following quotation:

Two freak examples of fracture occurred which were included, for the sake of convenience, among the composite fractures of the vault and base. The force which produced them, however, was unusual. The persons in question fell, striking on the vertex of the head, and both sustained fractures of the base, around and just anterior to the foramen magnum. There was evidence that the weight of the body, transmitted through the spinal column, forced the articular process of the occiput up through the base of the skull for a short distance.

73. Brun,<sup>2b</sup> case 156, fig. 144, p. 328.

74. Poulain, J.: Mécanisme et classification des fractures de la base irradiées à plusieurs étages, *Arch. gén. de chir.* 8:884, 1912; first fracture, fig. 12, p. 898; second fracture, fig. 21, p. 899, and third fracture, fig. 38, p. 911.

75. Sharpe, N. W.: Piston Action of Vertebral Column Developed in Certain Types of Cranial Fracture, *Bull. Johns Hopkins Hosp.* 29:281, 1918.

76. Reuter, K.: Ueber die Folgen der Einwirkung Stumpfer Gewalt, in *Lochte: Gerichtsarztliche und polizeiärztliche Technik*, Wiesbaden, J. F. Bergmann, 1914, fig. 118, p. 444.

Vance has no illustrations of these fractures. Among his diagrams of types of fractures is an incomplete and a complete ring.<sup>77</sup>

The foregoing brief from the literature on ring fractures embraces 45 more or less complete ring fractures; 23 were caused by headlong falls of some distance so as to strike head first; 1, that reported by Phelps, by a fall on the sidewalk; 1, by a fall so as to alight on the feet; 4, by blows on the head and 1, by head-crushing; 8 were produced experimentally and there is no information as to the mode of production in 7. The noteworthy feature is that 23 were caused by falls from several feet or more. The review is probably not exhaustive, but it indicates the relative frequency of observations of ring fractures up to modern times, the consideration they have received and the way they have been explained. In our series of 80 fractures there are 5 ring fractures of the vault and 36 of the base. Some of the latter are large; others are small.

#### REVIEW OF THE FRACTURES IN OUR SERIES

*Large Ring Fractures of the Base of the Skull (20).*—This type of ring fracture splits from the skull a large concave disk in the base, mainly of occipital bone, with the center of the disk near or opposite the top of the spine (1 to 15, and 16 to 20).<sup>78</sup> The ring is often finished behind by traumatic diastasis of the lambdoid suture, in front by fissures coursing in the petrous bones lengthwise, or along their ventral borders, and across the body of the sphenoid bone or transversely through the firm union between this bone and the basilar occipital plate. Externally, the rings run close to the base of the petrous bones, and a number are continued forward by diastasis of the parietotemporal sutures. Exceptions to this ground plan occur, more of them with the lateral than with other parts of the ring. The ring is sometimes narrowed so that the fracture is obliquely or more directly across one or both petrous bones, but its front and back locations remain fairly constant. Occasionally, removal of the front slightly to the rear brings this part across the basilar plate (4 and 10), but this is rare as compared with the frequency of invasion of the petrous bones. In only 1 of this group of 20 skulls was the fracture so low behind that the ring was all in the base, and in this cranium comminution split the ring and the other parts of the fracture were in the calvarium (13).

On the other hand, lateral deviations from the remarkable symmetry of 1 fracture (1) were fairly common. They varied widely from a narrowing which left the middle fossae intact (3) to asymmetrical

77. Vance,<sup>1</sup> fig. 3 D and E, p. 1028.

78. From here on numbers in the text used as these are indicate the fractures in figures 5 to 9 and the cases in tables 1 to 5, inclusive.

fractures of the petrous bones (3, 4, 10, 12 and 18) and to large ring fractures with some comminution of the base (14, 15 and 18). A few of the large ring fractures were not quite complete behind (8, 9, 10 and 11); others (3, 16 and 17) were incomplete in front. In the base of 1 skull (17) a huge ring fracture enveloped the middle fossa ventrally. Behind where it joined the back ring, both were incomplete on this inner surface. A word of caution is necessary at this point, because relatively few examinations were made of the *outside of the base of the cranium*,<sup>79</sup> and some ring fractures that were imperfect in the internal table owing to a small gap may have been completed in the external layers of the base. Many descriptions of fractures in the literature leave no doubt that the entire skull was available for study. Accompanying the accounts by some authors there are illustrations from which one may infer that the skulls were museum preparations. On the other hand, it is true that the conditions in the outside of the base are seldom mentioned. In the calvarium, absence of symmetry comparable with that in the base was occasionally encountered, and sometimes the top piece was comminuted (5, 6, 7, 13, 14, 15 and 20). In the base extensions ran forward from a few ring fractures (12, 14, 15, 17, 18 and 20), and a few such ventral extensions were sagittal in either the base (14) or the vertex (19). In 3 of the 20 skulls, there were independent fractures of the orbital roofs (2, 4 and 9). More or less loosening of an entire petrous bone is fairly common with basilar fractures; in fact, it is more frequent than is intimated by the particulars concerning the 20 large ring fractures. Breaking away of the posterior clinoid processes from the rest of the sphenoid bone (1, 2, 3, 8, 13 and 20) has been a subject of frequent comment by many observers. It is said that they are pulled away by the tug of the tough tentorium cerebelli when the sagittal axis of the base is lengthened by violence. Another feature of interest, also usually accredited to the careful observations of Félizet,<sup>15</sup> is the firm union between the apex of the petrous bone and the portion of the basilar plate of the occipital bone to which it is applied and the strong connection with the body of the sphenoid formed by the fibrocartilage of the carotid canal. These symphyses usually prevent traumatic diastasis of the petrous apices, and fractures in that region commonly cross so as to break off the inner third of the petrous bone. This portion of each bone with the basilar plate and a zone about the foramen magnum including the occipital

79. If the back flap of the scalp is dissected from the skull all the way down to the spine, and the skull disarticulated from the atlas, it may be dislocated and tilted so that the base is perpendicular and faces dorsally. The course of fractures in the inferior surface is then easily seen. The skull is replaced on, and wired tight to, the top of the spine, and no external sign remains to indicate the thoroughness of the examination.

TABLE 1.—Data on Fractures in Figure 5

No., Sex,* Age	Weight, Height	External Injuries	Injuries of the Brain; Length of Fracture, etc.	Circumstances, Observations, etc.
1 ♂ 30 yrs.	112 lbs. 5 ft. 4½ in.	Laceration of the scalp, 24 mm. long, its center 5 cm. cephalad to theinion; bruised buttocks	Tears of the inferior surface of the frontal lobes, the front tip of the right frontal lobe, inferior surface of the right temporal lobe and base of the left temporal lobe; length of fracture, 54.5 cm.	A fall down stairs; bleeding from the left ear; bloody spinal fluid; coma; right-sided facial paralysis; in the hospital 77 hours, 5 minutes; diagnosis, skull fracture
2 ♂ 40 yrs.	112 lbs. 5 ft. 1 in.	Fresh bruise, 15 mm. in diameter, 5 cm. above and 2 cm. to the right of theinion; bruised right hand, and bruised tissues overlying the coccyx and right scapula	Bruised tips of the frontal lobes; torn left temporal lobe and bruised outside of the left cere-brum; traumatic hemorrhages in the pons; the left tympanum torn; blood in the left middle ear; independent fractures of the orbital roofs; length of main fracture, 73 cm.	A fall downstairs striking the cement floor; walked back up stairs; bleeding from one ear; death en route a few hours later
3 ♂ 9 yrs.	47 lbs. 3 ft. 11 in.	Bruises behind each ear, above and below the left eye and of the right hand and leg; fractured right tibia, fibula and clavicle	No noteworthy gross injury of the brain; length of fractures, 42 cm.	Struck by a street car and dragged some dis-tance; fractured right leg; bleeding from the nose and ears; in the hospital 77 hours, 5 min-utes; diagnosis, skull fracture
4 ♂ 32 yrs.	142 lbs. 6 feet	Abrasions above each eyebrow, of the right cheek and of the left angle of the mouth; fractured right 8th rib	Torn frontal poles of the cerebrum, left tem-poral lobe; contusion of the right temporal lobe, and of each half of the cerebellum; length of fractures, 33 cm.	Struck by a street car; blood in the nose; coma; lessened corneal reflexes and strength in the right extremities; in the hospital 6 hours, 10 minutes; diagnosis, basal fracture
5 ♂ 70 yrs.	147 lbs. 5 ft. 8½ in.	No fresh external injury anywhere of the outside of the body	Contusion of the anterior pole of each frontal lobe; torn superior longitudinal sinus of the dura; length of fractures, 49.5 cm.	A fall in a livery stable; blood and cerebro-spinal fluid from the ears; stupor; vomiting; involuntary defecation; in the hospital 7 days; diagnosis, skull fracture
6 ♂ 43 yrs.	160½ lbs. 5 ft. 8 in.	Vertical abrasion of the nose, 17 by 3 mm.; hemorrhage in the deep scalp tissues behind; no external injury of the scalp	Top of the brain red from trauma; lacerated left frontal lobe tip; smaller lacerations of the right and left temporal lobes; length of fracture, 62.5 cm.	Found unconscious on the street bleeding from the ears and nose; pupillary reflexes absent; coma; bloody spinal fluid under pres-sure; in the hospital 8 hours; diagnosis, skull fracture
7 ♀ 42 yrs.	137 lbs. 5 ft. ½ in.	Blood in the deep scalp tissues behind; bruised left knee, right hand and arm; no external injury of the scalp	Small tears in the tips of each occipital lobe behind; subarachnoid hemorrhage anterior to the fissures of Rolando in the midline of the top; fluid blood in both middle ear cavities; length of fractures, 73.5 cm.	Hit by a touring car and removed unconscious from the street; death en route to the hospital

8 ♂ 63 yrs.	140 lbs. 5 ft. 2 in.	Brise behind the right ear; abrasion near the outer canthus of the left eye; abrasion of the right foot; fractured left femur; six right and two left ribs fractured	Bruised external surface of the right side of the cerebrum and incrimated left frontal lobe; length of fracture, 38 cm.	Struck by a motor truck; in shock on entrance with vomiting and bloody cerebrospinal fluid from the left ear; in the hospital 73 hours, 35 minutes; diagnosis, skull fracture and fractured left femur
9 ♂ 20 yrs.	71½ lbs. 5 feet	Superficial abrasions of the left leg and right buttock; no external injury of the scalp	Bruised tips of the left temporal and of each frontal lobe; blood in the untold air cells; empty middle ear cavities; independent fractures of the orbital roots; length of midline fracture, 42 cm.	An assault; incoherent on entrance; bleeding from the ears; normal pupils; bloody spinal fluid; in the hospital 12½ days; diagnosis, skull fracture and alcoholism
10 ♂ 67 yrs.	103½ lbs. 5 ft. 6½ in.	Bruised right arm and elbow, and the right side of the face	Bruises with hemorrhage in both frontal and both temporal lobes; length of fracture, 72 cm.	A fall on the sidewalk; coma; bleeding from the left ear; bloody spinal fluid; rigid neck; involuntary urination; in the hospital 3½ days; diagnosis, skull fracture
11 ♂ 51 yrs.	110 lbs. 5 ft. 7 in.	Scalp torn 3 cm. in the right and 4 cm. above the ilion; lacerations of the right wrist, the back of each hand and elbow, and above the right eye	Top tips of both frontal and both temporal lobes; length of fracture, 49.5 cm.	A fall "down some steps"; coma; bleeding from the nose, mouth and left ear; very bloody spinal fluid; all reflexes absent in the extremities; in the hospital 25 hours, 35 minutes; diagnosis, skull fracture
12 ♂ 31 yrs.	169½ lbs. 5 ft. 8½ in.	Abrasion 8 mm. in diameter, its center 10 cm. cephalad and 9 cm. dorsal to the left external auditory meatus; torn right lung; slight bilateral hemothorax	Bottom and sides of the right frontal and temporal lobes bruised and soft; length of fracture, 59 cm.	Hit by an automobile; coma; bleeding from the nose, mouth and right ear; linced extremities; lessened reflexes; bloody spinal fluid; in the hospital 15 hours, 55 minutes; diagnosis, basal skull fracture
13 ♂ 17 yrs.	114½ lbs. 5 ft. 2½ in.	Abrasion of the scalp, 2 by 4 cm., its center 2 cm. cephalad and 1 cm. to the right of the ilion; abrasion 2 cm. to the left of the vertex, 15 by 5 mm.; bruises about the left elbow of the left shoulder and of the right elbow	Bruised outside of the left occipital lobe; bruised front tip of the right cerebral hemisphere; length of fracture, 71.5 cm.	Fell from an automobile; coma; unequal pupils; blood in the right ear, nose and pharynx; bloody spinal fluid; in the hospital only 55 minutes; diagnosis, skull fracture, right middle fossa
14 ♀ 35 yrs.	115 lbs. 4 ft. 11 in.	Bruises 6 cm. above the opening of the left ear; bruised lower lip, left side of face and forehead, lower extremities, and left shoulder; fractured mandible, right tibia and fibula; fractured 5th cervical vertebra and fifteen ribs	Blood in the leptomeninges of the left cerebral hemisphere and bottom of the right temporal lobe; brain not bruised outside; 517 Gm. of blood in the left pleural cavity; blood in the middle ear cavities, sphenoid and ethmoid sinuses	Struck by a taxicab; pronounced dead in the receiving room of the hospital
15 ♂ 68 yrs.	133 lbs. 5 ft. 8½ in.	No external marks of violence; five left and seven right ribs broken	Bruised tip of the right frontal lobe, the inferior surfaces of the left frontal and temporal lobes, and the right hemisphere of the cerebellum; length of fractures, 70.2 cm.	Fell by an automobile; persistent bleeding from the left ear; pupils dilated; eyes fixed; muscular twitching; bloody spinal fluid; Cheyne-Stokes respiration; in the hospital 6 hours; diagnosis, basal skull fracture

\* In this and the following tables, ♂ indicates male and ♀, female. Length of fracture means total length of all the fractures.



condyles constitute the "centre de résistance" of Félizet. This is illustrated by 5 fractures (4, 10, 11, 17 and 18) which broke the petrous bones across near the apex on one or both sides. Diastasis between these bones and the basilar plate at the front end of one ring (3, 7, 11 and 15) is more common in smaller ring fractures.

*Small Ring Fractures of the Base of the Skull* (16).—The transition between large and small ring fractures about the foramen magnum is gradual. The ring in fracture 21 (fig. 6) was a little narrower from side to side, and the ring in fracture 3 (fig. 5) was also narrow, but in the remaining 15 (22 to 31 and 33 to 37, inclusive) the rings were definitely smaller. In this series of only 36 more or less complete ring fractures symmetry was not as common in the small as in the large ring type. In a larger number, this relation may be reversed. Only 3 (29, 36 and 37) of the 16 small ring fractures were fairly symmetrical. Two of these (29 and 36) were associated with more or less comminution of the base. The third ring fracture (37) was incomplete in front in at least the inner table. Gaps in 3 other small ring fractures (21, 24 and 31) also may have been bridged across by fissures in the outer table. A fourth ring fracture, incomplete behind, is shown in fracture 22 (fig. 6), but ventrally in the two front fossae there was a unique symmetrical ring enclosing the lesser wings, body and a large part of the greater wings of the sphenoid bone. Another equally remarkable feature of the injuries of this cranium was the trivial involvement of the calvarium, as compared with the fragmentation of the base. Another base with many fragments is shown in fracture 26 (fig. 6), but in this skull long fractures radiated from behind up in the vault. Fractures 23, 27, 28 and 33 also were continued in the vault, but for such short distances (about equal to the extensions in the skull cap in case 22), that their diagrams are omitted. In the ring fracture depicted by Sharpe,<sup>75</sup> the fissures within the ring forming a V-shaped fracture of the pars basilaris are the counterpart of that shown in fracture 30.

In another skull (28), this part of the occipital bone was broken transversely. The rings are very small in the fractures represented in 34, 35 and 36. Bruns,<sup>80</sup> and subsequently Senn,<sup>81</sup> emphasized the danger of sudden death, sometimes days after the accident, from wounds of the medulla oblongata or other parts of the brain stem which are caused by fragments loosened from the rim of the foramen magnum (26, 31 and 36). These shocking terminations are said to result from such movements as a sudden turning of the head to one side. This admonition by Bruns and Senn was based on accounts by Bell<sup>27</sup> of

80. Bruns,<sup>14</sup> p. 295.

81. Senn, N.: Fractures of the Skull, *Am. J. Surg. & Gynec.* 14:43, 1900.

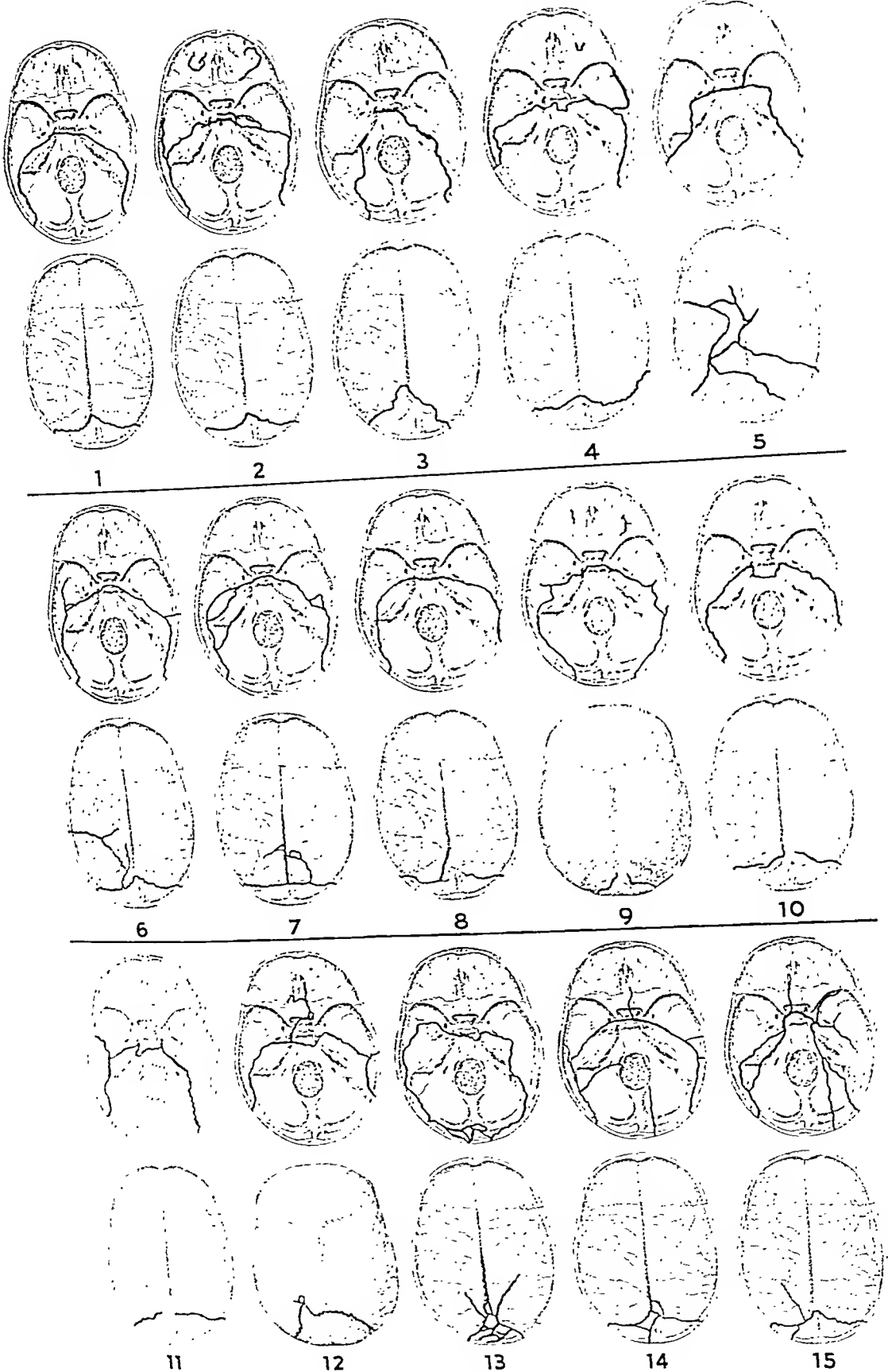


Fig. 5.—Large ring fractures of the base of the skull.

TABLE 2.—Data on Fractures in Figure 6

No., Sex, Age	Weight, Height	External Injuries	Injuries of the Brain; Length of Fracture, etc.	Circumstances, Observations, etc.
16 ♂ 32 yrs.	123 lbs. 5 ft. 8 in.	Horizontal laceration of the scalp, 28 mm. long, 4 cm. above theinion, its right end in the midline; bruised back of the left hand; small bruise of the back	Bruised inferior surface of the frontal and temporal lobes; blood in the lateral and 4th ventricles; blood in the right middle ear and right ethmoid cells; length of fracture, 54.5 cm.	A fall downstairs; death soon after entrance to hospital; diagnosis, skull fracture
17 ♂ 27 yrs.	130 lbs. 5 ft. 3 in.	Lacerated wound 6 cm. long above the left eye; bruised left cheek	Bruises of the brain, all dorsal; blood in the orbital tissues; subcutaneous emphysema of the front of the neck; length of fracture not recorded	Hit by a street car; decompression operation on the right temporal fossa; in the hospital 38 hours, 50 minutes; diagnosis, skull fracture
18 ♂ 3 yrs.	26½ lbs. 34 inches	Top of the head bruised; bruise in the deep scalp tissues above the right ear	Scattered microscopic hemorrhages in the brain generally; diastasis of the dorsal end of the sagittal suture 7 cm. long (not shown in the chart); on the left side, a part of the horizontal fracture in the outer table only; length of fracture, 71 cm.	Fell two stories striking head first on a cement court; coma; swollen left occipital region; blood in the pharynx; in the hospital 24 hours; diagnosis, skull fracture
19 ♂ 27 yrs.	118½ lbs. Height not recorded	Scalp wound 10.5 cm. above and 1 cm. dorsal to the right ear, two stitches; no other external injury	Bruised frontal lobes, more on the right side; blood in the right mastoid cells, bottom and front tips of frontal and temporal lobes; linear length of fracture, 69 cm.	Hit by a street car; coma; lacerated scalp; bloody spinal fluid; in the hospital 30 hours, 10 minutes; diagnosis, skull fracture
20 ♂ 38 yrs.	132½ lbs. 5 ft. 5½ in.	No external injury of the scalp; bruised left arm; fractured left ankle and left humerus	Bottom of the brain bruised, both sides equally; torn esophagus and left lung; left hemothorax; blood in both middle ears; length of fracture, 53 cm.	Hit by an automobile; coma; bleeding from the left ear; fractured left humerus and ankle bones; death 5 minutes after entrance to the hospital; diagnosis, basal skull fracture
21 ♂ 83 yrs.	165 lbs. 5 ft. 4 in.	One bruise 1 cm. to the right of the lambda; a second on the top of the head; both bruises small	Bruised frontal poles of the cerebrum; two small bruises of the left side of the cerebrum; length of fracture not recorded	Circumstances unknown; death in the Hospital of the House of Correction at the end of about 3½ days; irrational on admission; diagnosis, delirium tremens
22 ♂ 16 yrs.	97½ lbs. 5 ft. ½ in.	Extensive bruises of the face, more on the right side; fractured left femur	Medulla oblongata severed from the pons with a small splene of bone in the defect; brain bruises outside, mainly on the right and dorsal; torn apex of the left lung; left hemothorax (310 Gm.); length of fracture, 96.5 cm.	Hit by a motor truck; death en route to hospital
23 ♀ 45 yrs.	92 lbs. Height not recorded	Bruises of the right hand, right elbow and chin; also of both sides of the face, but more of the right side	Hemorrhage in the leptomeninges; brain not torn; 6th to 10th left, and 3d to 7th right ribs of fracture; thorax organs not injured; length of fracture not recorded	Hit by a street car; death en route to hospital
24 ♂ 36 yrs.	5 ft. 10 in. Height not recorded	Right wrist bruised; right tibia and fibula broken	Front poles of the cerebrum bruised; fracture entirely in the base; length not recorded	Circumstances not learned; blood in the right ear; in the hospital 24 hours, 35 minutes; diagnosis not recorded

25 Q 8 yrs.	45½ lbs. 46½ lb.	Blow, 13 by 15 mm. in diameter, 3.5 cm. above the inion; scattered bruises of the face, right arm and right buttock	One small bruise of each side of the cerebrum; large bruise of the cerebellum; blood in both middle ears, frontal, 91.5 cm. length of fracture, 91.5 cm.	Struck by a taxicab; diagnosis of depressed fracture of the left frontal region made in examining room where death occurred
26 Q 28 yrs.	114 lbs. 5 ft. 4 in.	Vertical narrow bruise, 2 cm. long, 6 cm. above and 3.5 cm. in front of the left ear; bruised left cheek and left elbow; fractured right leg bones	Blow of the left frontal lobe 6 cm. deep (front to back); multiple small hemorrhages in the pons; bruised left cerebellar hemisphere; length of fractures, 25.5 cm.	Hit by an automobile; pronounced dead in the receiving room
27 Q 30 yrs.	114 lbs. 5 ft. 3 in.	Horizontal tear of the scalp, 5 cm. long, and just below the inion, in the midline, and sewed with three stitches; bruised chin and left eyebrow	Both frontal lobes bruised, the right the more; bruises through the gray cortex into the white substance; length of the main fractures, 40 cm.; small independent fracture	Hit by a street car; coma; restless; bleeding from the right ear; contracted pupils with slow reactions; right nystagmus; bloody spinal fluid; in the hospital 6 hours; diagnosis, skull fracture
28 Q 41 yrs.	89 lbs. 5 ft. 2½ in.	Laceration 15 by 35 mm. at the level of the inion and a little to the left; bruise of the left side of the forehead; small bruises of the left knee, left shoulder and the right leg	Body decomposed; base of the skull in two lateral halves with the spine projecting into the skull; length of fractures, 87 cm.	Hit on the head with an ax (homemade); found dead
29 Q 10 yrs.	No records	Wound of the back of the head in the midline at the level of the lambdoid, slightly more on the right	Under surface of each frontal lobe bruised, the bruises small; small contusions of the bottom of each temporal lobe; blood in the right internal ventricle; length of fracture not recorded	Fell downstairs; unconscious and cyanotic; bleeding from the mouth, nose and right ear; right pupil dilated; death in the hospital 2 hours after the accident; diagnosis not recorded
30 Q 53 yrs.	113½ lbs. 5 ft. 2½ in.	Scalp torn for 2 by 4 cm., the long axis horizontal, all on the left side, at the inner end at the inion	Small bruise in each side of the cerebrum in the convolutions about the sylvian fissure (truncus fissurae lateralis); hemorrhage in the leptomeninges of the top of the brain; length of fracture, 85 cm.	A fall in the hospital while under treatment for acute alcohol poisoning; death 3 hours after the fall; diagnosis, acute toxic myocarditis
31 Q Age not recorded	89 lbs. 5 ft. 8½ in.	Horizontal laceration 4.5 cm. long, 1 cm. above and 4 cm. to the left of the inion; a vertical laceration 21 mm. long in the skin covering the left supra-orbital ridge and close to the midline	Extensive hemorrhage in the spinal leptomeninges ended in fractured vertebra; bruised spinal cord	Circumstances not learned; no history obtained
32 Q 30 yrs.	105 lbs. 5 ft. 5½ in.	Bruise of the nose and one of the middle of the forehead; fractured third cervical vertebra	Left cerebellar hemisphere torn; small hemorrhages widely scattered in the brain; length of fracture not recorded	Found dead in an alley; circumstances not learned
33 Q 19 yrs.	165 lbs. 5 ft. 6 in.	Triangular wound from 18 to 20 mm. on each side in the scalp, 1 cm. to the left and 6.5 cm. above the inion	Leptomeningeal hemorrhage; no external bruises of the brain; one small hemorrhage deep in the pons; length of fracture, 46.5 cm.	Death soon after being crushed between the wheel of a wagon and a barn door; not under medical observation
34 Q 34 yrs.	147½ lbs. 5 ft. 4½ in.	Small purple bruise of the scalp 4.5 cm. to the right of and 3 cm. above the inion; three bruises of the face; blood in left ear	Small contusions of the inferior part of each temporal lobe; length of fracture, 56 cm.	
35 Q 28 yrs.	123 lbs. 5 ft. 5½ in.	No external injury of the head except an abrasion behind the right ear; blood in the left ear		

two such deaths. One occurred after it was supposed that the man had fully recovered. He died suddenly "as if he had been pithed . . . . The margin of the great foramen magnum of the occipital bone was fractured, and it appeared that on suddenly turning the head, the condyle was displaced and the loose bone brought to press and nip the medulla oblongata." The other <sup>82</sup> death occurred while the head was being shaved by one attendant, and the patient was being bled by another. The latter noticed that the blood no longer flowed; "the loose portion of bone had been turned upon the spinal marrow, and crushed it." In the head of a man examined by Beck <sup>83</sup> "the bone between the jugular foramen and the margin of the foramen magnum on each side was splintered into several fragments . . . an entirely separate fracture was found in the region corresponding to the condyles of the occipital bone. . . . On pushing the fragments up into the skull the opening of the foramen magnum was considerably narrowed, and this seems to have produced the injury to the floor of the fourth ventricle." The man fell down a staircase that he was painting and was found standing on his head between the wall and the ladder. Shortly before Bruns explained this hazard from the small ring fractures, Trélat <sup>84</sup> also reported a similar unexpected death.

With impartial disposition of fractures on each side of the skull, one might expect a similar balance in the distribution of the occasioning force. So far as the large ring fractures in our series of 80 are concerned (tables 1 and 2, cases 1 to 20, inclusive), the evidence of violence compressing the skull vertically against the spine is not overwhelming.

In only 1 fracture of the group of 20 do the conditions match those commonly described for ring fractures. This was a fracture produced by a headlong fall of some distance to a cement court (18). The fracture differs, however, from those usually described, because they are in adults, as a rule, and this fracture was in an infant 3 years old, and also because most of the reported ring fractures caused by similar accidents have been close to the foramen magnum. This infant's scalp was bruised on top. With each of 5 other fractures in the group of 20 (1, 2, 11, 13 and 16), the scalp injury was close to the inion, and there were contrecoup contusions of the brain at the front end of the cerebral hemi-

82. Bell, C.: *The Nervous System of the Human Body*, ed. 3, London, Longmans, 1844, observation 149, p. 403. Both observations by Bell are mentioned by Chassaignac: *Lésion traumatique du crâne et des parties qu'il contient*, Thèse du concours, Paris, 1842, p. 27.

83. Beck, M.: *Fracture of the Base of the Skull*, Tr. Path. Soc. London **24**: 181, 1875.

84. Trélat, U.: *Fractures du crâne*, Bull. Soc. anat. de Paris, series 1, **27**:213, 1852.

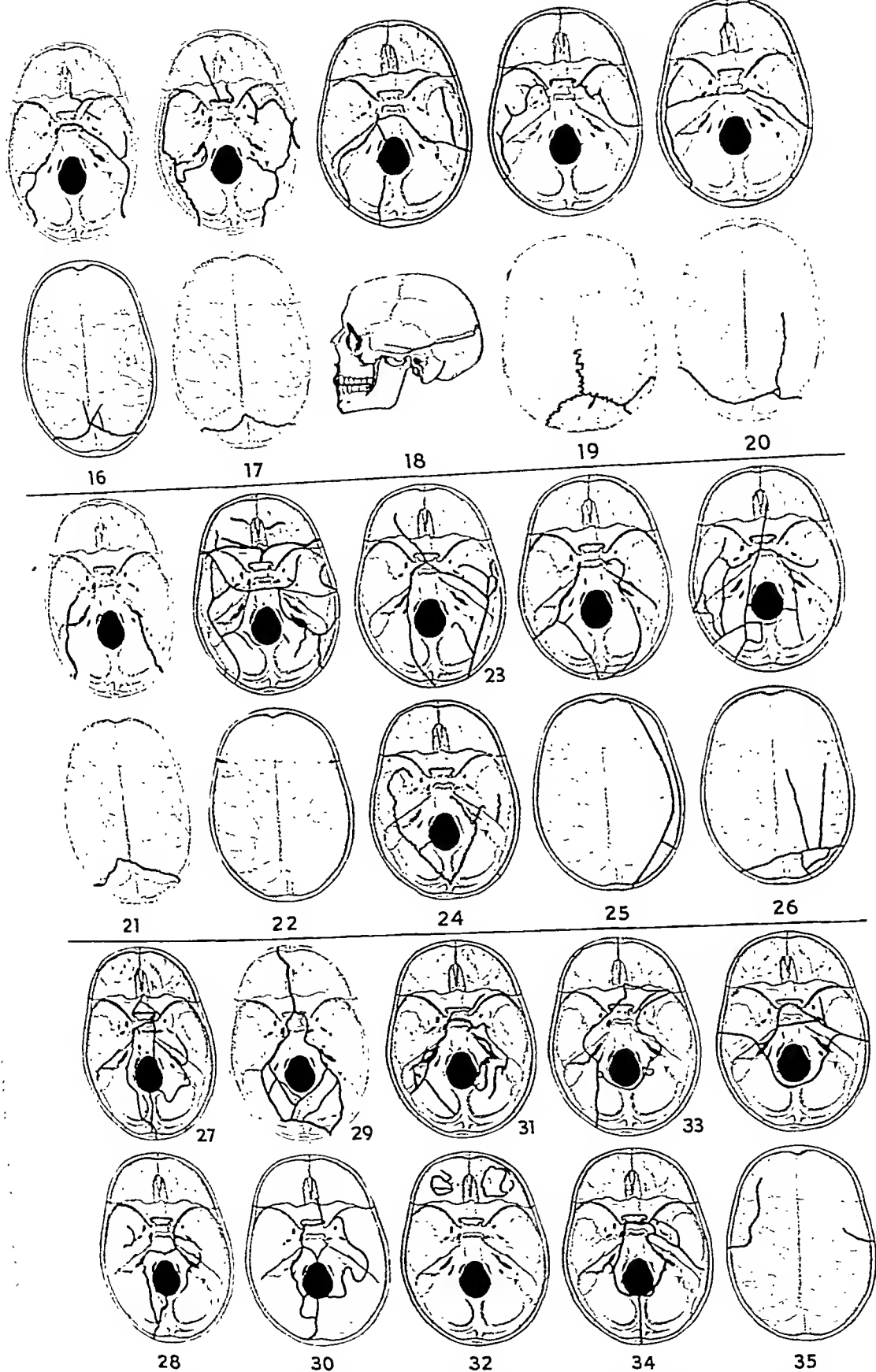


Fig. 6.—Large ring fractures of the base of the skull, gradually merging with smaller ring fractures. Solitary fractures of the orbital roofs are illustrated in 32. The dotted lines in 18 indicate the course of the fracture on the opposite side.

TABLE 3.—Data on Fractures in Figure 7

No., Sex, Age	Weight, Height	External Injuries	Injuries of the Brain; Length of Fracture, etc.	Circumstances, Observations, etc.
36 ♂ 40 yrs.	135 lbs. 5 ft. 7 in.	Bruise 5 cm. in diameter opposite theinion with a laceration in the center of the bruise "down to the bone"; two smaller bruises of the right side of the forehead; bruised right elbow, right knee, left groin and hand	Torn inferior surface of both frontal and of both temporal lobes; also of the vermis of the cerebellum; length of fracture, 89.6 cm.	Hit by an automobile; coma; bloody spinal fluid; in the hospital 33 hours, 20 minutes; diagnosis, anterior basal skull fracture
37 ♂ 30 (?) yrs.	148 lbs. 5 ft. 5½ in.	Lacerated wound 2 cm. in diameter, 1 cm. to the right of theinion; small bruise of the right elbow	Bruised inferior surfaces of both frontal and both temporal lobes, the bruises much larger on the left side; length of fracture not recorded	Circumstances not learned; bleeding from the nose and pharynx; coma; wound of the scalp; in the hospital of the House of Correction 7 hours, 10 minutes; diagnosis, basal skull fracture
38 ♂ 72 yrs.	115 lbs. 5 ft. 7 in.	Laceration of the scalp 3 cm. to the right of theinion with radiating tears (4) from 2 to 5 cm. long; three small lacerations of the left side of the face; purple left eyelids; fracture dislocation of the 5th and 6th cervical vertebrae	Superficial bruises of the inferior surfaces and deep bruises of the medial surfaces of both frontal lobes; a deep bruise in the right occipital lobe; bruised right temporal and parietal lobes (lateral surface); bruised top of the corpus callosum; length of fracture, 38.1 cm.	Hit by an automobile; deep coma; unequal pupils; rigid extremities; bloody spinal fluid; in the hospital 5½ hours; diagnosis, skull fracture
39 ♂ 55 yrs.	132½ lbs. 5 ft. 6¾ in.	Horizontal, irregular, deep tear of the left eyebrow 1 inch long; bruises and abrasions of the left side of the face and left side of the scalp ventrally; small contusions of both legs, the left arm, right foot and right hip; three left ribs fractured; fractured right pubis and ischialic bones	Simple "traumatic lividity" of the brain, i. e., hemorrhage in the leptomeninges; length of fracture not recorded	Hit by a taxicab; coma; small equal pupils; blood in the nares; bloody spinal fluid; in the hospital 2 hours, 45 minutes; diagnosis, skull fracture
40 ♂ 25 yrs.	89 lbs. 5 ft. 3 in.	Eyelids purple from orbital hemorrhage; bruised right knee; 70 Gm. of blood between the dura and the calvarium on the left side, the clot 2 cm. thick	Superficial bruises of the lower frontal and temporal convolutions of each side and of the inferior surface of both frontal and temporal lobes; compressed brain; one fracture 27.5 cm. long; the other, 28.1 cm.	Hit by a taxicab; coma and dyspnea; restlessness; bloody spinal fluid; in the hospital 44 hours, 50 minutes; diagnosis, cerebral concussion, suspected skull fracture
41 ♂ 63 yrs.	116 lbs. 5 ft. 7 in.	Vertical laceration of the front of the right temporal fossa; the scalp abraded 4 cm. to the right and 6 cm. in front of theinion; abrasion of the left cheek; fractured 6th cervical vertebra, pubis bones, left tibia, left fibula and three left ribs	Many small superficial bruises of the inferior surface of both frontal and both temporal lobes; length of fracture, 46.6 cm.	Hit by a taxicab; bleeding from the nose; coma; in a first aid hospital 5 hours, then in Cook County Hospital 4 hours; diagnosis, lacerated scalp and fractured leg bones
42 ♂ 30 yrs.	120 lbs. 5 ft. 4 in.	Right side of the chin bruised; surgical incision of the scalp above and behind the right ear	Small contusion of the under surface of the cerebrum; length of fracture not recorded	Circumstances not learned; comatose; in the hospital 3 hours; diagnosis, suspected skull fracture

Circumstances not learned; no history or diagnosis obtained

41	W, not taken 5 ft. 2 in. Youth	Contused left side of the head; left femur fractured at the upper end	Fractures began 2.5 cm. above and 1.2 cm. below the left auditory meatus, and ended in an exactly corresponding place in the right side; length of fractures not recorded	Injured by an automobile; coma; bleeding from the left ear; frequent vomiting; right decompression operation; in the hospital 92 hours; diagnosis, skull fracture
42	106 lbs. 5 ft. 2½ in. 9 12 yrs.	BruiSED right elbow, cheek, lip and right side of the nose; severe contusion above the left ear; decompression wound of the right side of the head	Entire under surface of the right temporal lobe; small part of the opposite temporal lobes; extensive hemorrhages into the leptomeninges; extensive central infarct of the cerebellum; length of fracture not recorded	A fall down a stairway was the verdict of a coroner's jury; found dead
43	200 lbs. 6 feet 15 (about)	Blood in both ears, the nose and mouth; bruised right elbow; fracture courseD through external auditory canal	Superficial bruises of the under surface of both temporal lobes, the front pole of each frontal lobe and the back of the right occipital lobe; length of fracture not recorded	Struck by an automobile; coma; bleeding from the nose, ears and mouth; in the hospital 15 hours, 15 minutes; diagnosis, skull fracture
44	115 lbs. 5 ft. 1 in. 10 yrs.	Two lacerated wounds of the right side of the head, one 13, the other 10, cm. long; a third 7.5 cm. long above and behind the left ear; three small lacerations of the back of the ear; right hand; bruises of the left cheek; fractured sternum	Scattered regions of hemorrhage in the leptomeninges; no gross contusions of the brain; blood in both middle ears; length of fracture, 63.7 cm.	An automobile accident; deep coma; closed eyes; bleeding from the nose and both ears; pupils inactive; in the hospital 3 hours, 15 minutes; diagnosis, basal skull fracture and shock
45	202 lbs. 6 ft. ½ in. 30 yrs.	Lacerated wound 2.6 cm. long, 7.5 cm. above the opening into the right ear; bruises of the outer end of the right eyebrow, right side of the forehead and right leg; eleven fractures in seven right ribs; both innominate bones broken in front, more on the right	Hemorrhage in the leptomeninges covering the back end of each occipital lobe, the upper surface of the left occipital lobe and the bottom of the cerebellum on each side; length of fracture, 31.5 cm.	Thrown from an automobile when a tire exploded; sluggish dilated pupils; stertorous breathing; bleeding from nose and both ears; bloody spinal fluid; in the hospital 5 days; diagnosis, basal skull fracture
46	91 lbs. 5 ft. 0½ in. 48 30 yrs.	Two large abrasions of the left side of the face and one of the left ear; bruised back of each hand and right foot	Two large and two small bruises of the outside of the right temporal lobe; bruised right frontal lobe, medial surface and gyrus cinguli; extensive leptomeningeal hemorrhage; length of fracture, 35.5 cm.	Circumstances not learned; comatose; bloody cerebrospinal fluid running from the left ear; blood in the mouth; dilated pupils; in the hospital 2½ hours; diagnosis, basal skull fracture in the middle fossae
47	137 lbs. 5 ft. 8½ in. 45 yrs.	Two lacerated wounds above and behind the left ear, the longer 3 cm. long; a small bruise of the left side of the forehead, another of the right elbow and a third of the left knee	Small superficial bruises of the right frontal and right temporal lobes; length of fracture, 21 cm.	Struck by a steel car; irrational; no bleeding anywhere except from the scalp wound; in the hospital 3 hours, 35 minutes; diagnosis, scalp wound and scullity
48	123½ lbs. 5 ft. 5½ in. 73 yrs.	Small laceration (1 cm. long) in the scalp in the front part of the left temple; large bruises of the back of each elbow	Deep bruises of the right parietal lobe; a small bruise of the back part of the right inferior temporal convolution; length of fracture, 37 cm.	Automobile collision; coma; bleeding from the nose, mouth and ears; labored breathing; depressed bone felt above the right ear; in the hospital 21½ hours; diagnosis, skull fracture
49	117 lbs. 5 ft. 3 in. 21 yrs.	Bruises and abrasions of each side of the head; three small perforating wounds of the scalp above and behind the right ear; fluid blood in both middle ears; left tympanum torn	Extensive bruising of the right central convolutions of the parietal region; multiple small hemorrhages throughout the pons; length of fracture, 15 cm.	Slugged by burglars with a hammer; coma; paralyzed right arm; sluggish pupils; stiff neck; swelling behind the left ear; bloody spinal fluid; in the hospital 39 hours; diagnosis, skull fracture
50	143½ lbs. 5 ft. 8½ in. 30 yrs.	No external injuries, but the scalp was partly where bleeding from the skull fracture had occurred; blood in the middle ears, ethmoid and subconjunctival sinuses and in the orbital fat; bruised right knee and arm	Scattered superficial contusions of bottom and both sides of the cerebrum, the largest in the right temporal lobe; length of fracture not recorded.	



spheres, indicating that when violence broke the skull, the head was in motion and was arrested at that moment.<sup>4a</sup> In 6 other bodies (4, 5, 6, 9, 10 and 15), there were contrecoup brain bruises at the front tips of the frontal lobes, but no scalp injuries. One man (9) was assaulted; another it was said, fell on a sidewalk (10). The distance of the fall in another case (5) was not learned. Street traffic caused the other 3 accidents (4, 6 and 15). The way blows at or near the occipital boss make large ring fractures about the foramen magnum will be discussed when small ring fractures are reviewed. But it is well at this time to emphasize the existence of evidence of violence to the back of the head in both of the last two groups, 11 fractures altogether. In one group, the evidence consisted of scalp injuries and contrecoup brain bruises; in the other, simply brain bruises.

Five of the 20 large ring fractures were less symmetrical than the others (8, 12, 14, 17 and 19). The brain bruises were also less symmetrical, which accords very well. In all 5 bodies, the scalp injuries were definitely on one side, an observation in accord with the first two. In order to explain the ring fractures at the base in these 5 craniums, it is necessary to assume that the head was twisted in some manner when hit. The course of events, let us say, for the man 63 years old (8), was possibly as follows: His first injury was close to the outer angle of the left eye. By this, he was unbalanced, and his head was turned to the right. Then he fell so that the scalp was bruised behind the right ear. The lagging brain received a contrecoup bump at the anterior end of the left cerebral hemisphere. But the accompanying large ring fracture is almost symmetrical. If it was caused by the oncoming weight of the trunk driven against the base of the skull, it seems plausible that the head at the time was swung around by, and on, rotating cervical vertebrae, so that compression against the spine was from behind the right ear. Applying this notion of a bent head to another of this group of 5 fractures (17), in which the contrecoup bruises were in the back poles of the brain and the external wound was above the left eye, one may suppose that the head was thrown well back and a little to the right when the man hit something face first, and the blow of the spine on the base of the skull made the fracture.

Two other large ring fractures (3 and 20) may have been produced entirely by violence to the base of the skull. There are no positive indications of this; in fact, both fractures resulted from vehicular accidents. It rather staggers belief that blows from vehicles may so project bodies that the only force applied to the skull is by way of the spine. On the other hand, bones of the lower extremities were broken in both bodies. The boy's head (3) was bruised on each side, but the

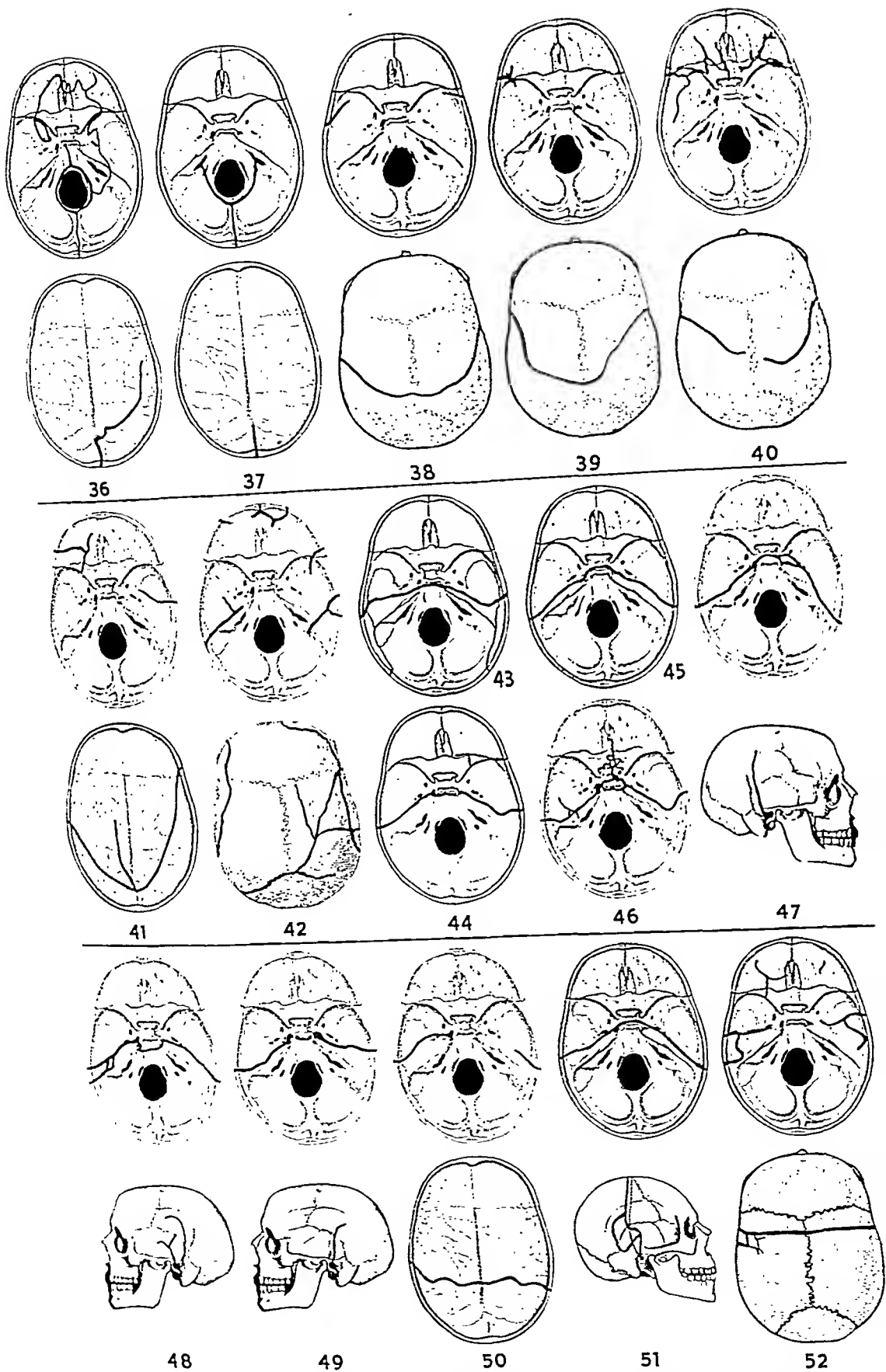


Fig. 7.—Small ring fractures of the base (36 and 37), ventral ring fractures of the vertex (38 to 42) and dorsal transverse incomplete and complete fractures (43 to 52). The dotted lines in 47, 48, 49 and 51 indicate the location of the fractures on the opposite side.

TABLE 4.—Data on Fractures in Figure 8

No., Sex, Age	Weight, Height	External Injuries	Injuries of the Brain; Length of Fracture, etc.	Circumstances, Observations, etc.
53 ♂ 41 yrs.	95 lbs. 5 ft. 10 in.	Lacerated wound 15 mm. long above the outer end of the left eyebrow; both temples purple from deep bleeding; bruised upper left arm; sacral bed sore	Extensive but superficial bruises of the right middle and inferior temporal convolutions; torn dura; extradural clot (17 Gm.) compressing the right frontal lobe; acute fibrinous meningitis; length of fracture, 45.9 cm.	Hit by an automobile; mentally confused; spinal fluid clear; time in first hospital not learned; in Cook County Hospital 11 days; diagnosis, skull fracture
54 ♂ 38 yrs.	178 lbs. 5 ft. 9 in.	Lacerated wound 6.5 cm. long up and back from the outer end of the right eyebrow (7 stitches); bruised right side of the face; bruised back of each hand	Hemorrhage in the leptomeninges of the top and side of the left cerebral hemisphere; small bruise of the right frontal and large deep bruises of the left parietal lobes; blood in the lateral ventricles; length of fracture, 17 cm.	Run over by a horse and wagon; coma; left outer strabismus; bleeding from the nose; tongue deviated to the right; blood in the throat; lower extremities rigid; vomiting; bloody spinal fluid; in the hospital 30 hours, 20 minutes; diagnosis, basal skull fracture
55 ♀ 40 yrs.	102 lbs. 4 ft. 10½ in.	Large abrasion of the right side of the face; fractured mandible 4 cm. to the left of the midline; "black and blue" eyes; bruised left thigh	Minute bruise of the right upper temporal convolution; a larger bruise of the gyrus rectus of the right frontal lobe close to the olfactory trigon; generalized fibrinopurulent leptomeningitis; length of fracture, 42.5 cm.	Run over by an automobile; comatose and restless; bleeding from the nose and ears; absent patellar reflexes; recovered consciousness and complained of headache; in the hospital 7 days; diagnosis, basal skull fracture
56 ♂ 31 yrs.	120 lbs. 5 ft. 5 in.	Deep abrasion of the left temple 4 by 2.5 cm.; bruised ears; lacerated wound 1 cm. long in the upper attachment of the right ear; a small abrasion behind the right ear; another on the right side of the forehead; lacerated left upper arm; bruised knees; six fractures in twelve ribs; five left ribs fractured; hemothorax	Three small contusions of the side of the right and one of the left cerebral hemisphere; bruised anterior tips of each temporal lobe; bruised traumatic hemorrhages in the pons and one hemorrhage 8 by 5 mm. in the right thalamus; length of fracture, 42.8 cm.	Fell from a third story porch; coma; profuse bleeding from the mouth and nose; bloody spinal fluid; in the hospital 65 minutes; diagnosis, fractured skull and ribs
57 ♂ 60 yrs.	94 lbs. 5 ft. 1½ in.	Bruise of the right temple 8 by 12 cm.; bruised right upper arm, shoulder, right leg and right side of the trunk	Large deep contusion of the left temporal lobe; length of fracture, 52 cm.	Fell over a stair railing; stupor at first; irrational later, slight bleeding from the left nostril; dilated sluggish right pupil; lacerated tongue; in the hospital 9 days; diagnosis, skull fracture
58 ♀ 28 yrs.	140 lbs. 5 ft. 2½ in.	Irregular laceration 8.5 cm. long in the scalp on top of the head; opposite the coronal suture and transversely directed (8 stitches), most of it on the right side; incised wound of the calvarium and dura	Large deep wound of the top of the brain opposite that in the calvarium; a piece of bone 18 by 12 mm. in the brain wound, length of fracture, 23.7 cm.	Hit on the head with an ax; semiconscious; brain tissue, blood and hair in the wound of the head; flaccid general paralysis; uncontrolled sphincters; bloody spinal fluid; in the hospital one week; diagnosis, open wound of the head and brain

	Weight not recorded	Hypodermic scars (morphine) of the abdomen; no fresh external injuries	No injuries of the brain; hemorrhage in the scalp at the vertex, 9 by 6.5 cm.; dura unbroken; length of transverse dibrasis, only 2.5 cm.	Circumstances not known; sent to the hospital of the House of Correction with delirium and fever; in the hospital 1 day; diagnosis, meningo encephalitis
29 ♂ 40 yrs.	5 ft. 3½ in.	Large purple bruise of the forehead on the right side; bruises of the back of each arm, the back of the left hand and inside of the left leg	Deep bruises of the bottom of the frontal lobes and top of the parietal lobes, the former much the larger; superior longitudinal sinus not torn; an extradural hemorrhage (51 cm.) opposite the top of the frontal lobes due to torn small emissary veins; length of fracture, including the dibrasis, 22 cm.	Fell in the hospital while under treatment for alcoholism; swollen scalp on one side; in the hospital 66 hours, 55 minutes; death 41 hours after the fall; skull fracture suspected
61 ♂ 31 yrs.	121 lbs., 5 ft. 5 in.	Surgical decompression wound of the left side of the head; bruise above the left eye; fractured left hip; large open wound of the left upper arm; loose fragment of bone in the wound; fractured left clavicle	Extradural symmetrical hemorrhage from the glabella to the lambda widest (5 cm.) at its front end; traumatic leptomeningeal hemorrhage ventrally; at the front end the fracture runs in only the outer table to the left supra-orbital ridge; dura not torn; length of fracture not recorded	Collided with an automobile while riding a motorcycle; delirious; fractured humerus; in the hospital 72 hours, 35 minutes; diagnosis, fractured left humerus; skull fracture suspected
62 ♂ 31 yrs.	150 lbs., 5 ft. 4 in.	Horizontal bruise-abrasion, 9.5 by 3.5 cm., across the forehead, almost symmetrical but a little more on the right side; bruised right elbow, forearm and hand; fractured 8th to 11th left rib inclusive	Front poles of the temporal and frontal lobes bruised; bruises of the bottom of both frontal lobes; the bruises all superficial but extensive; dura not torn; length of fracture, 25.7 cm.	Hit by an auto truck; restless; coma; ster-torous breathing; fractured ribs; pupils active; knee jerks slow; bloody spinal fluid; in the hospital 4 hours, 10 minutes; diagnosis, suspected skull fracture
63 ♂ 5 yrs.	37½ lbs., 45½ inches	Lacerated wound 4 cm. long close to the inflexion in the scalp; small bruises of both sides of the forehead; left decompression surgical wound; bruised right leg	Deep bruises of the top of each frontal pole of the cerebrum; small bruises of the bottom of the frontal and temporal lobes; small extradural clots opposite the sagittal suture; sagittal sinus intact; length of fracture, 29 cm.	Hit by an automobile; coma from which he later could be aroused; decompression operation shortly before death; in the hospital 72 hours, 10 minutes; diagnosis, skull fracture
61 ♂ 40 yrs.	129½ lbs., 5 ft. 4½ in.	Vertical deep laceration of the scalp 4 cm. long, 2 cm. to the right of the incision; four small lacerated wounds of the right and one of the left side of the face; a bruise of the top of the head on the right side; laceration of the head on the right external angular process of the frontal bone, floor of the right orbit and superior maxilla; fractured left humerus; five right and two left ribs fractured	Many small superficial bruises of the top and bottom of the frontal lobes, of the bottom of both temporal lobes ventrally and both inchete gyri; traumatic hemorrhages in the left putamen; length of fracture, 49 cm.	Hit by an automobile; unconscious with a "dissecting hematoma" under the scalp; in the hospital 2 hours, 35 minutes; diagnosis, basal skull fracture
65 ♂ 30 yrs.	180 lbs., 5 ft. 8 in.	No external injury except purple upper eyelids from deep bleeding; blood in the nostrils, esophagus and large air passages	No gross hemorrhages in the brain anywhere; extensive hemorrhages in the leptomeninges of the top of the head; dura not torn; length of fracture not recorded	A fall downstairs; deep coma; bloody spinal fluid; in the hospital 2½ hours; diagnosis, basal skull fracture
66 ♂ 15 yrs.	141½ lbs., height not recorded	Three bruises of the back of the head close to the inflexion; right deep pupillary hemorrhage	Large deep lacerations of the under surface of the frontal and front part of the temporal lobes; one minute hemorrhage in the nose; dura not torn; length of fracture not recorded	Fell off a truck, landing head first on a pavement; able to walk but "dazed"; later unconscious; in the hospital 21 hours, 10 minutes; diagnosis, suspected skull fracture

street car had dragged him some distance. His brain was not bruised outside, a condition common with skull fractures in children. The man (20) was 38 years old and was hit by an automobile at a street crossing. Although no bones of the trunk were broken, the esophagus and left lung were torn. According to the necropsy record: "About the junction of the esophagus and diaphragm, there is a blood-stained region including the adjacent lung which is irregularly torn from the entrance of the left bronchus to the diaphragm, so that the branching of the pulmonary vein is seen in the bottom of the tear." The tear in the esophagus was small, in line with the tear in the lung and at the diaphragm. The bruises of this brain were confined to the parts in contact with the base of the skull. Obviously of greater importance are the character of the fractures and the absence in each body of injuries of the scalp in the midline.

Evidence to explain another large fracture ring (7) is even less satisfactory. One knee was bruised; the scalp was not injured outside. The little loose blood it contained was only 1 mm. thick,<sup>85</sup> opposite the fracture, with its inner limit at the pericranium and obviously from torn vessels in the bone. The injuries of the brain were behind and not contrecoup.

The 16 small ring fractures (21 to 31 and 33 to 37, inclusive) may also be examined in groups. With 11, there were associated scalp injuries about the lambda. This is a larger proportion than the 5 in the group of 20 large ring fractures. Because the numbers are small, this difference may have no significance. Another variation is the fewer contrecoup bruises at the front poles of the cerebrum as compared with the frequency of similar contusions of the brain accompanying the large ring fractures. Study of the tables will also disclose more bruises of the bottom of the brain with the small, than with the large, ring fractures. But these are trivial particulars contrasted with the evidence pointing to the production of 23 of the total number of 36 ring fractures,<sup>86</sup> both large and small, by violence applied to the back of the head and not, as one would expect, to the vertex. This evidence, as has been stated, consists of contusions of the scalp at or close to the inion and injuries of the front pole of the cerebrum. Each supplements the other

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85. In order to decide whether blood free in the scalp results from external violence at that place or is from vessels in the bone torn by the fracture, parallel cuts close together should be made from the inner surface of the reflected scalp outward, and almost, but not entirely, through the scalp.

86. Among the large ring fractures, 1, 2, 11, 13 and 16; 4, 5, 6, 9, 10 and 15; among the small ring fractures, 21, 25, 27, 28, 29, 30, 31, 33, 34, 36 and 37 with dorsal scalp injuries and 24 with deeply bruised tips of the frontal pole of the cerebrum but no scalp injuries.

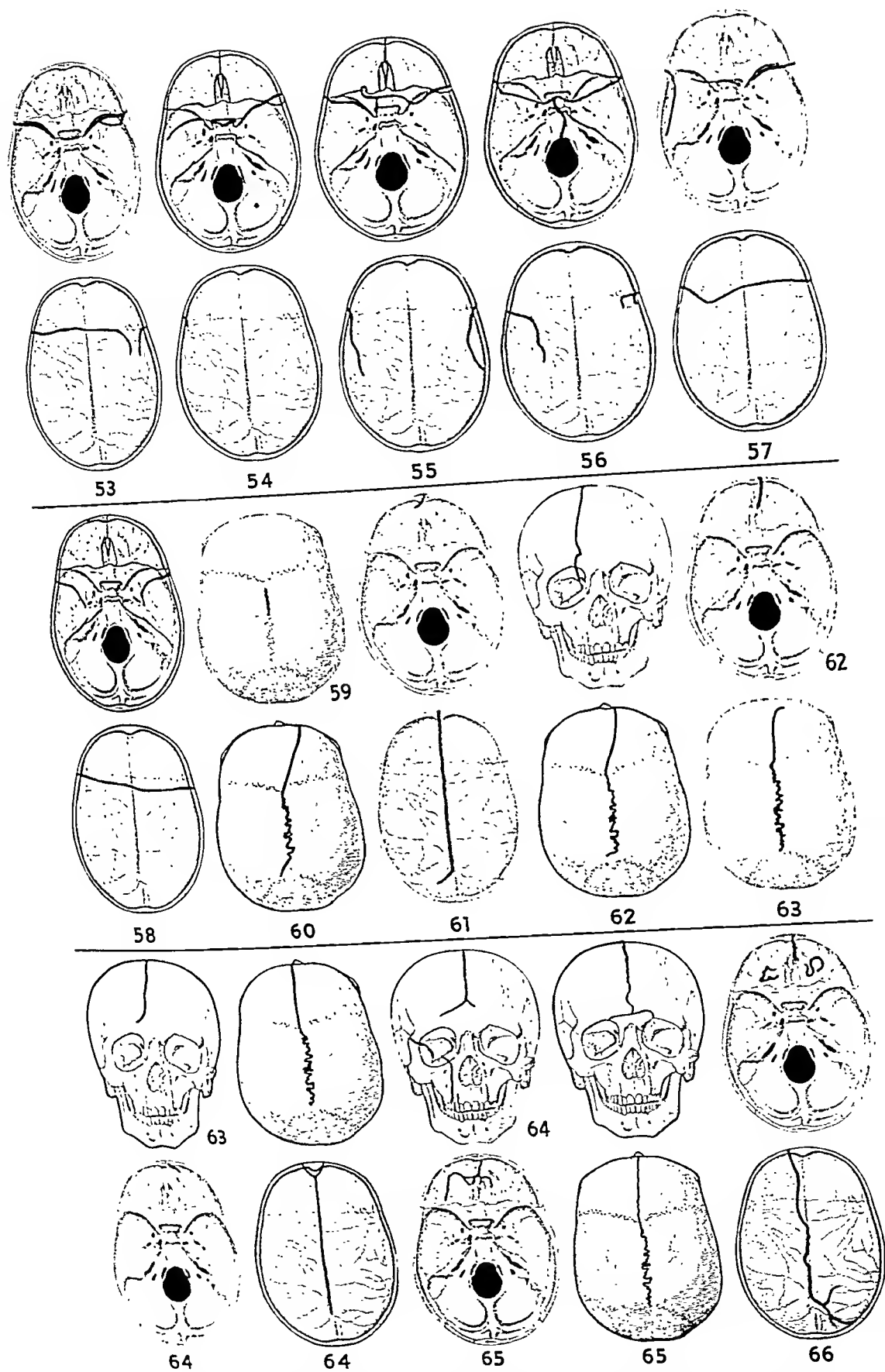


Fig. 8.—Ventral transverse incomplete fracture (53 to 58) and sagittal fractures of the vault (59 to 66). For fracture 64, there are four figures; for both 65 and 66, three, the third diagram of 66 being in figure 9.

TABLE 5.—Data on Fractures in Figure 9

No., Sex, Age	Weight, Height	External Injuries	Injuries of the Brain; Length of Fracture, etc.	Circumstances, Observations, etc.
67 ♂ 52 yrs.	130 lbs. 5 ft. 1½ in.	No external injury; large hemorrhage in the scalp on top of the head, presumably due to bleeding from the broken bone	Bruise 2 cm. deep of the frontal pole of the left cerebral hemisphere; extensive hemorrhage in the leptomeninges; dura intact; length of fracture not recorded.	Fell down a flight of stairs when drunk; admitted to hospital 16 hours later; coma; the right arm at the mouth; pupils inactive; eyes to the right; arms spastic; reflexes lessened or absent; in the hospital 21 hours, 45 minutes; diagnosis, uremia
68 ♂ 30 yrs.	148 lbs. 5 ft. 10½ in.	No fresh or recent external injury; large hemorrhage of practically the entire top of the scalp, bregma to inion, 19 cm. wide	Twenty grams of blood between the dura and calvarium; the top along dural sinus intact; contusions of the bottom of each frontal lobe at the tip and smaller bruises of the front end of each temporal lobe; length of fracture, 20.5 cm.	Circumstances not learned; noisy coma; pupils unequal and fixed; lower extremities and right arm rigid; all reflexes except those of the left arm absent; bloody spinal fluid; in the hospital 18 hours, 45 minutes
69 ♂ 31 yrs.	225 lbs. 6 ft. 5½ in.	A repaired surgical (?) cut 11 cm. long in the scalp across the back of the head, 12 cm. above the inion	Bruises of the under surface of the frontal lobes, 4 by 2.5 cm., with smaller bruises of the frontal lobes elsewhere; small contusions of the temporal lobes; dura intact; length of fracture not recorded	Circumstances not learned; bloody spinal fluid; in the hospital 5 hours 5 minutes, diagnosis, cerebral hemorrhage
70 ♂ 33 yrs.	119 lbs. 5 ft. 5 in.	Pale blue discoloration, 6 cm. in diameter, swollen from deep bleeding in the right half of the forehead; blood in the ethmoid cells	Deep bruises of the front poles of each frontal lobe and of the inferior surface of both frontal parietal lobes; multiple small bruises of the left pons; blood in the lateral ventricles; the dura intact; length of fracture, 25.5 cm.	Fell off street car; coma; entire scalp of the vertex edematous; bloody spinal fluid; convulsions; froth in the mouth; in the hospital 22 hours, 5 minutes; diagnosis, skull fracture
71 ♂ 28 yrs.	160 lbs. 5 ft. 8½ in.	Bruise of the back of the head in the midline 3 cm. in diameter; blood in the left nostril; swollen purple eyelids; torn liver; right hemothorax	Bruises of the lower surfaces of both temporal lobes; dura intact; length of fracture not recorded	Fell from a viaduct; coma; bleeding from the nose and mouth; flaccid extremities; sterotonic breathing; in the hospital only 30 minutes; diagnosis, skull fracture
72 ♂ 33 yrs.	98 lbs. 5 ft. 8 in.	Purple discoloration of the lids of both eyes and of the cheek adjacent to the right lower eyelid; left temporoparietal decompression operation	Deep bruise of the inferior part of the right occipital lobe of the cerebrum; fibrinopurulent leptomeningitis; superior longitudinal dural sinus intact; length of fracture, 28 cm.	Fell from an automobile when it struck a curb; decompression on the day of entrance; in the hospital 15 days; diagnosis, skull fracture

73 ♂ 30 yrs.	127½ lbs. 5 ft. 9 in.	Scalp of the forehead, eyelids, of the scalp in front and behind the ears and of the right side of the neck purple from deep bleeding; right decompression operation	bruises of the bottom of each frontal lobe; much smaller bruises of the bottom of each frontal lobe; acute fibromuscular meningitis; superior longitudinal dural sinus intact; length of fracture, 30.5 cm.	Found sitting on the sidewalk after a fight; delirious and could not walk alone; absent scrotal and abdominal reflexes; eye reflexes could not be obtained; involuntary urination decompression operation the day after entrance; in the hospital 9 days; diagnosis, skull fracture
71 ♀ 65 yrs.	100 lbs. 5 ft. 1 in.	One lacerated wound 10 in., and a second 12 mm. long, both above and behind the third 15 mm. long above and behind the right ear; a fourth opposite the left angle of the mandible; small bruises of the scalp; bruised right elbow	Superficial contusion with leptomeningeal hemorrhage of the entire lower surface of the left frontal lobe; smaller lesions of the right frontal lobe and front. of the right temporal lobe; length of fracture not recorded	Circumstances not learned; in the hospital only 1½ hours; diagnosis, skull fracture
75 ♀ 38 yrs.	122 lbs. 5 ft. 6 in.	Cruel laceration of the scalp in the occiput; bruised arms, forearms, left thigh, both legs and lower lip	Extensive and deep bruises of the inferior part of each frontal lobe; extensive leptomeningeal hemorrhage; length of fracture, 21.2 cm.	Found morning at the foot of a basement stairs; sent to the hospital of the House of Correction to be treated for alcoholism; deep coma; bloody spinal fluid; general muscular rigidity; in the hospital 40 hours; diagnosis, skull fracture
70 ♂ 35 yrs.	128 lbs. 5 ft. 0½ in.	Lacerated wound 3 cm. long just to the left of the midline of the vertex of the head	Contusions of the bottom of the frontal lobes near the midline; many contusions of the bottom of each temporal lobe, more of the left; multiple small traumatic hemorrhages in the pons; length of fracture, 26.5 cm.	Had a fit at home and fell, injuring the back of the head; convulsions; eyes deviated to the left; bloody spinal fluid; in the hospital 4 hours, 55 minutes; diagnosis, cerebral hemorrhage
77 ♂ 35 yrs.	131 lbs. 5 ft. 7 in.	Lacerated wound 2.5 cm. long and 1.5 cm. wide, 1 cm. above theinion, just to the right of the midline	Superficial bruises of the under surface of each frontal lobe, the top of the right parietal lobe and the under surface of the left temporal lobe; traumatic hemorrhages of both tentorial angle and the right cornu anatomic; length of fracture, 25.5 cm.	Knocked down (hanged?), his head hitting a pavement; picked up unconscious; unconscious until death; in the hospital 8 hours, 15 minutes; diagnosis, skull fracture
78 ♂ 16 yrs.	62 lbs. 4 ft. 4 in.	Deep bruise of the scalp at the occiput 5 cm. in diameter; two other smaller bruises of the scalp at the vertex; huge lacerations of the right thigh, lower part of the abdomen and genitalia	Small superficial bruises of each frontal lobe at the anterior poles; two minute contusions of each side of the cerebrum; length of fracture, 19 cm.	Ran over by a truck; extensive lacerations exposing the right femoral vessels; skin and superficial fascia torn from the lower part of the trunk; testicles bared; severe shock; in the hospital 1 hour, 35 minutes; diagnosis, shock and hemorrhage
70 ♂ 65 yrs.	114 lbs. 5 ft. 3 in.	Laceration 4.5 cm. long of the scalp, 1½ lower and 7 cm. to the right of, and 4.5 cm. above, theinion (2 stitches)	Bruises 2.5 cm. in diameter of the front pole of each frontal lobe; length of fracture, 10 cm.	Slipped on ice and fell; coma; boggy scalp; unequal pupils; noisy breathing; in the hospital 10 days; diagnosis, occipital basal skull fracture
80 ♀ 35 yrs.	88 lbs. 5 ft. 3 in.	Irregular X-shaped lacerated wound of the scalp, of the back of the head, 4 cm. long, 3 cm. to the right and 4 cm. above the horizontal level of the external auditory openings; bruised elbows and right arm and right thigh; blood in the right middle ear	Deep bruise of the front pole of the left cerebral hemisphere, a smaller one of the right; bruised under surface of the left half of the cerebrum; length of fracture, 31.0 cm.	Struck by a street car; unconscious; occipital vomiting; bloody spinal fluid; in the hospital 12 hours, 10 minutes; diagnosis, basal skull fracture



when together in the same body, but either alone suffices to indicate definitely the place where the force fracturing the skull is applied.

Persons afoot on the street, hit by street cars, automobiles and trucks, are knocked down and occasionally run over.<sup>87</sup> A few undoubtedly are violently thrown some distance, but they are seldom tossed up so as to come down head first and sustain scalp injuries of the vertex. On the other hand, head-first landings occur after ejection from vehicles in collision. But among the 23 fractures caused by violence applied to the back of the head, only 7 were produced by vehicular accidents. Eight persons fell. Presumably, the man assaulted (9) also fell. One, a woman (29), was hit on the head with an ax. For the remaining 6, the circumstances were not learned. So there is nothing uniform in the nature of the accidents. There are other factors, however, that presumably prevailed in all 23 casualties. The persons were alive when injured, with their heads, necks and trunks normally held together, their cranial cavities full of brain, cerebrospinal fluid and meninges, and all the intracranial blood vessels contained more or less blood. The head, when hit from behind, was not sent rolling away from the body. The neck held it fast, and at the lower end of the neck the weight of the trunk and extremities resisted.

Among those persons knocked down so as to fall backward, the backs of some presumably struck first, and the head, with increased centrifugal speed, struck immediately after. For others, these events may have been reversed, the head hitting first. In any case, the force applied to the back of the head in the midline was disposed, in order to make the ring fractures, either to drive the head down on the spine or to tear it away. That the latter deserves consideration is indicated by the impossibility, without fractures being produced somewhere, of forcing all the bony parts in the midline behind, from the occipital boss down to the level of the scapular spines, to lie in contact with a flat surface at the same time. In not one of the 23 ring fractures now under consideration was the neck broken. The cervical vertebrae held together, but the floor of the skull gave way to a force which, according to this view, was inclined to jolt the head away from the spine. Moreover, the floor of the skull broke where it also fractures when compressed vertex to spine or vice versa, that is, in its weakest places. When Quenu and Tesson<sup>86</sup> made the large ring fracture already referred to, an entire dead body was fastened to one of two heavy planks, but the plank extended only to the shoulders; the head was left free. The planks were fastened together end to end by a hinge. From an erect position, the body with its plank was forcibly thrown to the floor so that the

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87. Bacon, L. H., and Le Count, E. R.: *Automobile Injuries: A Study from Records of Postmortem Examinations*, Arch. Surg. 18:769 (March) 1929.

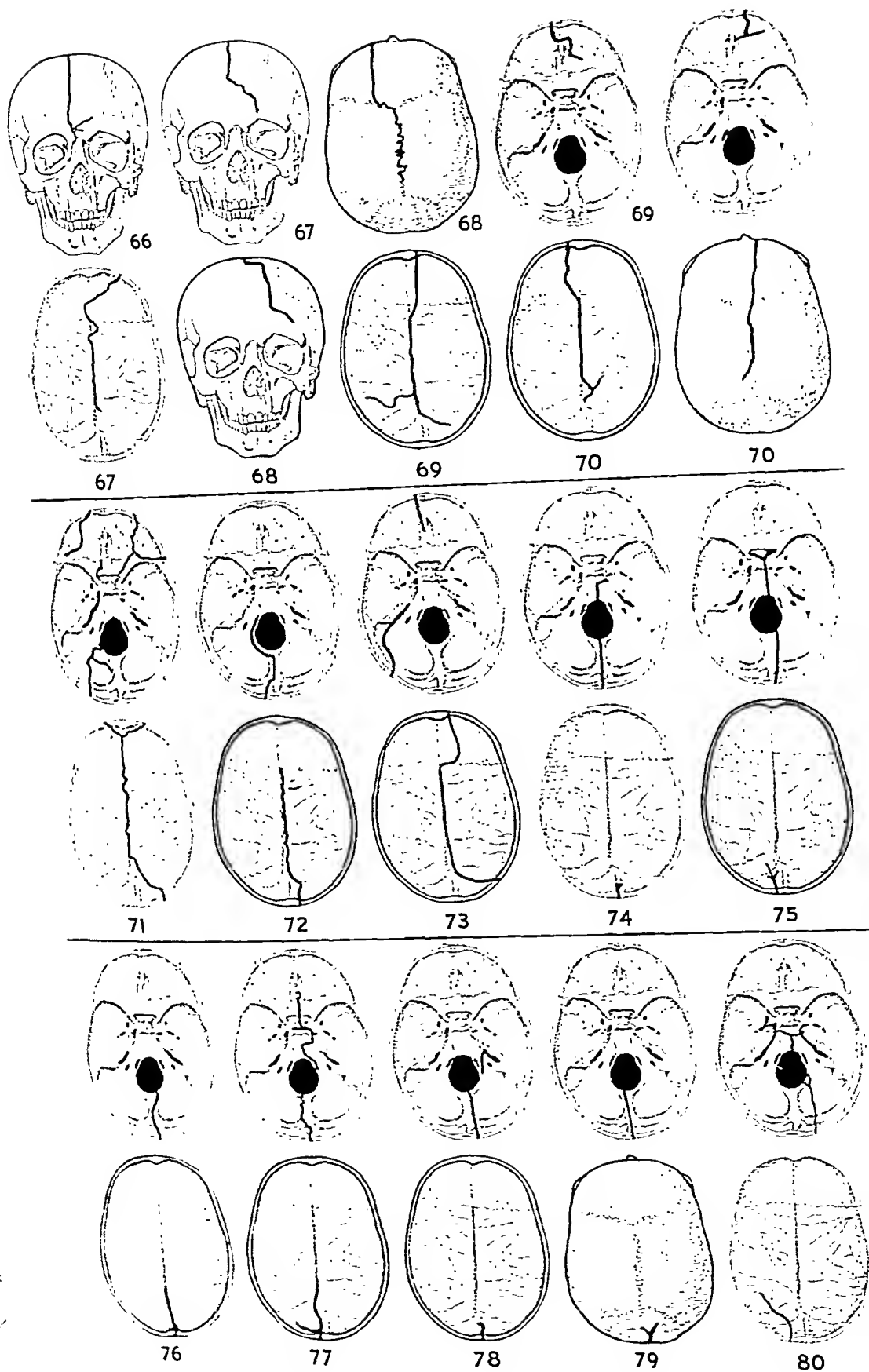


Fig. 9.—Sagittal fractures. There are three diagrams for fracture 70.

occiput struck the rim of a curbing; the large ring fracture produced had no branches.

In another place, mention is made of a ring fracture described by Bell<sup>88</sup> as a "pure instance of counter fissure," the blow being delivered on the back of the head of a man in a tunnel by a bucket that fell 50 feet (15 meters). One may well wonder what the position of the man was, how far forward his head was bent and whether he was erect or on his knees, so that the falling bucket was able to hit "the strongest part of the skull in the convexity of the occipital bone." Answers to these questions correlate with whether the bucket drove the head down on the spine or partly tore most of the head away from the spine when the ring fracture was made.

There remain for consideration 4 small ring fractures (22, 23, 26 and 35). Two of these (22 and 35) probably were fractures produced by crushing the head from side to side. In 1 case both sides of the head of the boy (22) were bruised severely in front of each ear. The prevailing transverse course of the fractures indicates that the head was run over. Both petrous bones were loose. Opposite the transverse fracture of the basilar plate of the occipital bone, the brain stem was *completely severed*. The slightly damaged skull cap is astounding when compared with the comminuted base. A second allusion to the symmetrical ring in the front half of the base of the skull is warranted on account of its uniqueness. With the other accident (35) came a circumstantial tale of the body being crushed between the wheel of a wagon and a barn door, and the head was the only injured portion. In this skull, the basilar plate was also fractured across well forward.

The third of these 4 fractures occurred when the front of the thorax of the woman (23) was apparently hit by the street car, for the fractures of the ribs were all close to the costal cartilages. She probably fell backward. Although the brain was not contused, the hemorrhages in the leptomeninges were on the frontal lobes. The fourth fracture was due to violence behind the left ear (26). A bruise there was the only external injury of the head; the asymmetrical enclosure of the foramen magnum by fissures is only a detail of severe comminution spreading from the site of trauma.

*Ventral Ring Fractures of the Vertex (5).*—Apparently these fractures have not received any special attention. Descriptions of them are exceedingly rare. One interesting account deals with the popular Duke of Orleans, son of Louis Philippe I, King of France. The Duke was thrown from a carriage on July 13, 1842, and died about five hours later.<sup>89</sup> The cranium was broken into upper front and lower

88. Bell, p. 467.

89. Editorial, *Lancette française*, Gaz. d. hôp. 15:433, 1842.

back portions by fractures on each side from the lambdoid suture forward and down in the middle fossae. The body of the sphenoid bone was broken across; the squamous part of the left temporal bone was loose and held in place only by soft tissues. Although other explanations were suggested,<sup>90</sup> Marchal (de Calvi) insisted that the Duke had fallen so that the back of his head on the left side first hit the roadway. In support of his contention, Marchal appeared before the Academy of Medicine<sup>91</sup> with a skull in which he had produced injuries similar to those in the head of the Duke. He had taken a cadaver and stood it erect on an amphitheater table. Facing it, he took it by the shoulders and hurled it to the floor so that the back of the head on the left side struck first. He described the resulting fracture as follows:

Cette fracture, qui s'étend de l'occipital, à droit et à gauche, jusqu'à la base du crâne en passant par le milieu de la selle turcique, et qui divise le crâne en deux moitiés, l'un inférieur et postérieur, l'autre antérieur et supérieur est semblable à celle du prince.

His demonstration created great interest at the Academy and is set forth here at length because, although the fractures in the Duke's head are referred to frequently in the older literature, their experimental duplication by Marchal has been generally neglected.<sup>92</sup> In both skulls there were ventral ring fractures of the vault, but the upper front portions broken away from the rest of each cranium, judging from Marchal's descriptions, were somewhat larger than similar portions in craniums 38 to 42, inclusive. Berchon<sup>93</sup> described a healed fracture that ran all the way around the top of the skull horizontally, but lower on the left side, below the occiput behind and through the left frontal eminence. Berchon found the skull in the museum at Rochefort. It was brought there from New Caledonia. In the cranium of a boy who died six months after a bicycle collision, Phelps<sup>94</sup> noted a healed fracture which extended "from the left temporal fossa across the forehead, three-fourths of an inch above the supraorbital ridge, to a point three-fourths of an inch internal to the right external angular process and then with a curve passed upward and inward to the median point of the

90. See the letters by Le Gros and Tanchou,<sup>89</sup> pp. 406 and 407.

91. Footnote 89, p. 432; see also: Marchal (de Calvi): *Relation chirurgicale de la mort du prince royal*, *Ann. de chir. franç. et étrang.* 5:465, 1842.

92. Marchal was evidently present in the little shop where the Duke died. His account of what transpired and mention of those present is touching and circumstantial. Guizot in the last volume of his "*History of France*" also described the distressing scene and said he was there three hours.

93. Berchon, E.: *Fracture circonscrivant presque régulièrement la voute du crâne d'un sauvage de la nouvelle calédonie, cicatrisation osseuse complète*, *Bull. Soc. anat. de Paris*, series 2. 8:95, 1863.

94. Phelps,<sup>100</sup> case 117, p. 466; case 51, p. 466, and case 82, p. 444.

coronal suture." The description he gave of the fractures in two other skulls also suggest ventral ring fractures of the vault. But there are no illustrations, unfortunately, and connected with the fractures of the vault there were other fissures radiating down in the lower half of the cranium. In the long analysis of skull fractures by Brann<sup>26</sup> there are illustrations of the course followed in 127 skulls by fractures of the type from which our 80 were chosen, but none is a ventral ring fracture of the vertex. Other contributions like this by Brann have been examined with similar results.

The first 3 of the ventral ring fractures of the vertex in our series (38 to 42, inclusive) were fairly symmetrical; the other 2 were decidedly less so. There were bruises and small lacerations of the left side of the face of one of these 5 bodies (38). The lower left incisor was freshly knocked out, the corresponding upper tooth loosened and the tongue torn. Directed obliquely across the head was a lacerated wound behind the right ear. The brain injuries were mainly of the bottom portion and in the frontal and temporal lobes. The front cerebral tips were not contused. The nature of these injuries together with the fracture-dislocation between the fifth and sixth cervical vertebrae indicates that the face was hit first and the man knocked backward; also that the head was in motion when it was arrested. Although the force breaking the skull was obliquely directed from behind forward and from right to left, the symmetry of the cup-shaped disk almost broken from the rest of the skull is remarkable. In the next head in this group (39), there were also contusions and small fresh tears of the face, mainly on the left side, but no other external injury of the head. There was a large bruise in front of the left ear on a third head (41), with a lacerated wound in the scalp covering the front of the right frontal fossa. If these injuries were produced by a side to side compression because the taxicab ran over the head, they probably were made after the skull was fractured, for the 3 fractures radiating forward from the lambda are unlike those produced by violence applied to the sides of the head. In the soft tissues of the other 2 heads (40 and 42), there were no external injuries except a curved surgical incision behind the right ear of 1 (42). Close to the bone blood had spread from the fractures in the deep scalp tissues of both heads and in the orbits and eyelids of 1 (40) where the floor of the frontal fossa was broken extensively. None of these 5 ring fractures was complete. In 4, the gap was at the front end; in the fifth (40), it was in the vertex. The bottom of each of the 5 brains bore signs of injuries in the front half; in 1 (39) there was simply leptomeningeal hemorrhage; in the others, contusions as well. There were no contusions at the front of the cerebrum in any of the 5 brains. Four of the fractures were caused

by motor vehicles. How the fifth (42) happened was not learned: it probably was a similar accident. "Alcoholism and suspected skull fracture" was the only recorded diagnosis.

The similarity of these fractures implies a force acting in the same direction for all 5. One of the bodies (42) came to necropsy with the head entirely shaved. Tops of 3 other heads were bald (38, 39 and 41). Under such conditions, had there been injuries of the outer layers of the scalp opposite the dorsal parts of the ring fractures, they would not have escaped notice. A fourth head (40) was that of a Mexican with coarse black hair 15.5 cm. long on top. The fractures in this cranium differed from those in the other 4. They were unconnected in the vault and comminuted in front. The natural inference that violence was applied to the face has no support from injuries there, for there was none. The eyelids were purple from bleeding which developed gradually in the hospital. Moreover, at the time of entrance there was "a lump over the right parietal bone." In the scalp of the fifth head (38), there was a lacerated wound on the right of the occiput, but the bruises of the face, as well as 3 broken ribs, were on the left side. Apparently the automobile struck the man in front, but more on the left side, knocking him down, and when the head hit the road the symmetrical ring fracture of the front portion of the vault was produced.

It is difficult to exaggerate the importance of the location of the brain injuries in any venture to understand how these 5 fractures were produced. Some brains bore bruises elsewhere, but the front half of the bottom of each was injured. The front tips of the cerebral hemispheres were uniformly unhurt grossly. These conditions have two definite implications: that the heads were in motion and that abrupt arrest and fracturing occurred when the back of the crowns struck something. One natural corollary is that 3 of the 5 heads, and possibly a fourth, struck soft or padded surfaces, and the scalp opposite the injured portion of the brain escaped injury.

In our review of the literature on ring fractures of the base of the skull there is abundant evidence of interest in the influence that the weight and the resistance of the trunk have in the production of the fractures. But the part played by the trunk mass in causing other varieties of cranial fractures has not received the attention it merits. A far greater and reprehensible neglect has been the failure to emphasize properly the importance of the face mass. In both particulars this disregard has been only relative.<sup>25</sup> We have been unable to find measure-

<sup>25</sup> Duret: Sur le mécanisme des fractures du crâne. Arch. gén. de chir. 6:689, 1930.

ments of the weight of the face mass. The mandible, other bones of the face and the soft parts of the face that we removed from one cranium soon after death weighed 815 Gm., but they were well drained of blood.<sup>96</sup> During life they probably weighed at least 2 pounds (0.9 Kg.). With the increasing momentum such a mass has at the end of a backward fall, its pressure on the bottom of the front end of the cranium must be considerable. If before the fall the body is thrown upward somewhat and in falling comes down head first and obliquely to the ground, as an arrow does at the end of its flight in target shooting, and the back part of the crown strikes first, conditions exist which may account for these ventral ring fractures of the vertex (38 to 42, inclusive). In these 5 skulls the parts below the ring fracture held fast, whereas the face mass tended to move on with the cranium above the fracture. Their momentum was not checked simultaneously with the rest of the head. The force was delivered obliquely near the occiput and in the midline, and the resulting ring fractures are obliquely and symmetrically disposed in the front end of the cranium. This explanation has some support from the presence of broken necks in 2 of the 5 bodies (38 and 41). With the other 75 fractures in our series, there were only 2 other broken necks (14 and 32).

*Symmetrical Fractures of the Orbital Roofs (6).*—In searching for accounts of ring fractures, we came across many records of asymmetrical independent and solitary fractures of the base of the skull. Their inclusion in a table, because of the historical value it would possess, was seriously entertained. But the number of such fractures observed is too large and, although intimately related, they are unlike our 80. We were able to foresee that in this omitted table there would be many short segments of ring fractures. Among about 90 of these asymmetrical fractures of the base of the skull we found 22 solitary or independent fractures in the petrous bones and 22 in the orbital roofs. Fourteen of the latter were on the right side and 4 on the left, and for 4 the side was not stated. We also found 11 reports of more or less symmetrical fractures in both orbital roofs with, in 9 of the skulls, fractures elsewhere in the cranium. In the 2 remaining,<sup>97</sup> the fractures were solely in the orbital roofs. This we encountered in our case 32; associated injuries were bruises of the nose and forehead and a fractured third cervical vertebra. The other symmetrical fractures of orbital roofs (2, 9, 22, 52 and 66) were associated, but unconnected, with fractures elsewhere in the cranium.

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96. The body was not embalmed.

97. Leriche: *Fracture du crâne; épanchement de sang à la base; kyste de l'arachnoïde*, Bull. Soc. anat. de Paris, series 1, 10:55, 1835. Vincent, E.: *Contribution à l'étude des fractures indirectes de la base du crâne et des lésions consécutives aux traumatismes cérébraux*, Alger méd. 15:141, 1887, case III.

The face mass probably had considerable influence in causing some of these. In 2 heads with fractures from falls (2 and 9), there were large ring fractures with contrecoup bruises of the front end of the brain. The fractures in 66 were also from a fall; they were sagittal in the vault, with the lower surface of the brain bruised in front. These 3 heads (2, 9 and 66) were in motion when broken. The vault of a fourth head (52) was hit by a hammer on the left side. The fracture was transverse, and the part enacted by the face mass was one of resistance, such as the spine exerts at the other end of the base of the skull. It has long been known that solitary fractures of the orbital roofs often are caused by blows on the forehead or elsewhere on the upper part of the face. Bouchacourt,<sup>98</sup> as long ago as 1840, in discussing a presentation by Taignot, commented on the facility with which this is accomplished on cadavers. The unevenness of the orbital plates causes them to buckle when axes are shortened.<sup>99</sup> Small fragments of thin, translucent bone remain attached to the dura when the bone is bared, and tags of orbital fat are forced in the cranial cavity. A violence of this sort caused the fractures in case 32.

Although it is always surprising to find the entire cranium or only its upper or lower halves split in two parts by either sagittal or more or less symmetrical transverse fractures, the experience is fairly common in postmortem examinations for medicolegal purposes. The fractures usually have direct paths easily reconciled with both the direction of the causal force and the site of its application. For these reasons, the attention given these fractures in medical literature is inconsiderable and devoted chiefly to recording their incidence. In this special group of 80 selected fractures, 38 are either transverse or sagittal. We shall restrict our discussion to the evidence obtained about the nature of the violence causing them, the way it acted and the degree with which this violence is reflected in the peculiarities of the fractures.

*Dorsal Transverse Fractures (10).*—The first 4 fractures in this group (43 to 46, inclusive) were in the base of the skull and were only about half way around. They extended so short a distance in the skull cap on each side that the sketches are not reproduced. In the next 3 skulls (47, 48 and 49), the fractures run a little higher, and their location is represented on diagrams of the sides of the skulls. The dotted lines represent the course on the opposite side. Two skulls (50 and 52) were broken almost in two, and 1 (51) was completely broken. In 3 (44, 48 and 49), the fracture ran across the front of the clivus.

98. Bouchacourt, in discussion on Taignot: Observation de fracture du crâne et de contusion du cerveau, Bull. Soc. anat. de Paris, series 1, 15:37, 1840.

99. This inbending was demonstrated experimentally by Chipault and Braquehay.<sup>25</sup>



There is no need to recapitulate what has been written about fractures of this kind. They are not uncommon, and it has been quite generally accepted for many years that they are caused by force applied to the sides of the skull. The manner in which 2 of the 10 fractures (43 and 49) were sustained was not learned. One (45) was due to a fall; another (50), to being hit by a street car; another (52) resulted from slugging by burglars, and motor vehicles caused the remaining 5 (44, 46, 47, 48 and 51).

Our interest concerns the external injuries and the injuries of the brain and the bearing that their location has on the character of the fracture. The information about 1 body (43) is too defective, and no external injuries were present on a second (45), except a bruise of the back of the right elbow. Such bruises are very common on the bodies of persons who fall backward or who are knocked down. Some of the bruises of the brain of this body (45) were at the front end. It was said this man fell downstairs. His head may have hit more than once.

Interpretation of what happened when 3 other bodies were injured is beset with difficulties. One of these (47) was the body of a man 6 feet tall (182.9 cm.), weighing more than 200 pounds (90.7 Kg.). A lacerated wound was found in the right temple; there were 11 fractures in 7 ribs on the right side; the right innominate bone was broken in its pubic and ischiatic portions, and the left pubic bone was broken close to the midline. The right side of the forehead and right eyebrow were bruised. The most reasonable explanation is that when the man was hit he fell forward, bruising the face and the back (contrecoup) of the brain; then he was run over so that the ribs, pelvic bones and skull were fractured. The alternative is that all the injuries of the right side, including the fractures, were first received when he was struck by the automobile, and that subsequently a fall forward injured the face and brain. The automobile that another man (51) was driving at a high rate of speed collided with a truck. In the pons, there were multiple minute hemorrhages indicating severe impact. This is supported by the loosening of a fragment of the calvarium above and behind the right ear. Another possibility is that when the skull broke, the front and back fragments bent a little, the one on the other, for the fracture ran all the way around, and that when bending occurred, the pons was bruised. But scattered small hemorrhages are frequent in the pons from trauma<sup>100</sup> when the skull is not broken in two, and they accompany fractures which fail to correspond to any special pattern. Absence of injury of the left hemisphere indicates that the head was not moving

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100. In this connection see the article by Greenacre, P.: Multiple Spontaneous Intracerebral Hemorrhages, *Bull. Johns Hopkins Hosp.* 28:86, 1917.

at any considerable rate of speed from left to right when the blow was received that broke out the piece behind the right ear. The left cheek was bruised, and this, with the absence of contrecoup bruising of the brain, points to a side-to-side compression of the head.

As for the third body (52), a Negro whose head was hit on the left side with a hammer by burglars, the sole question concerns bruises antipodal to the region of comminution in the left side of the skull cap. The outside of each temporal lobe and the bottom of both the frontal and the temporal lobes were bruised, the bruises on the right side being much larger than those on the left. It would seem, therefore, that after the man was slugged, he fell so that the left side of the head struck. This assumption involves the possibility of a localized fracture of the left side of the head made with the hammer, and a transverse fracture, almost complete, due to the fall. Injuries in the other 5 bodies (44, 46, 48, 49 and 50) are accounted for easily. Brain injuries were more marked or limited to the right side in 4 bodies (44, 48, 49 and 50), and there were external injuries of the left side of each head. In the fifth body (46), these conditions were reversed. In other words, both the external and the cerebral wounds corroborate trauma to one side of the head.

*Transverse Ventral Fractures (6).*—It seems that these side-wise circular fractures prevail in the bottom half of the skull. Of the 10 dorsal fractures just reviewed, 7 were incomplete in the vertex and 2 in the bottom. Of the 6 ventral sidewise fractures, 4 had their gaps in the skull cap (53, 54, 55 and 56); 1 was unfinished in the bottom (58), and 1 was probably complete (57). Fracture 53 was almost complete. Of particular interest is the sagittally directed fracture in 1 head (56) from the sella to the front rim of the foramen magnum. With 4 of these 6 ventral ring fractures (53, 54, 56 and 57), there were injuries of the outside of the head on one side, usually farther forward than those accompanying the dorsal transverse fractures. In each of these 4, there was sufficient bruising of the brain opposite the external wounds of the head to stamp it as indirect. These 4 heads were in motion when struck, and the movement was in paths connecting their external injuries with the opposite brain contusions. One of these bodies was that of a man who, it was said, was run over by a horse and wagon (54). His injuries conform simply to those inflicted by being struck down. There were tales of falls concerning 2 other cases: in 1 the fall was over a stair railing (57) and in the other, from a porch on a third floor (56). In the latter body, the injuries of the trunk were severe.

In another instance it was said that the woman (55) was "run down by an auto." Apparently, the fractures of the cranium and mandible were

produced when the wheel of the machine passed over her head, for the brain bruises were on the right side where there was a huge abrasion of the face; the fracture in the lower jaw was opposite. The rarity of this grouping of injuries of the head and brain is worthy of comment. The last of these 6 ventral crosswise fractures (58) is of even greater interest, because it was made with an ax. A portion of the fracture was a cut with some small fragments of bone at its site.<sup>101</sup> One of the fragments had been driven into the deep wound in the top of the brain. One remarkable feature of the injury of the head was that the long dimension of the edge of the ax was directly across the top of the head.

*Sagittal Fractures (22).*—The remaining fractures in our series of 80 are mainly or altogether in the sagittal plane. The symmetry is of fragments, not of fracture lines. The first 12 (59 to 70, inclusive) were mainly or altogether in the vault; the next 3 (71, 72 and 73) were in the vault and base, and the rest (74 to 80, inclusive) were exceedingly basilar. Judging solely from the inner surface of 1 cranium (69), there were independent fractures in the orbital roofs; in another (61), the bones of the face were broken on the right side; lengthwise fractures of the clivus were present in 4 (74, 75, 77 and 80); in 4 heads (61, 63, 72 and 73), there were unilateral surgical decompression wounds of the scalp and cranium. A history of a fall is quite common with sagittal fractures. One man (70), it was said, fell from a street car; another (77) was knocked down in a fight; a third (73) was found sitting on a sidewalk after a fight; 1 of the 4 women (75) was found moaning at the foot of a stairway; for 7 others (60, 65, 66, 67, 71, 76 and 79) the history of a fall was even more definite and reliable. This makes a total of 11 fractures due to falls. Six of the remaining 11 (61, 62, 63, 64, 72 and 78) belong under the caption of accidents from motor vehicles; another (80) fracture resulted from being hit by a street car, and the circumstances for 4 (59, 68, 69 and 74) were not learned.

At present, there seems to be no reason for dealing separately with these sagittal fractures, because some were basilar and others were in the dome. In fact, comments on the mechanism of their production follow rather simple patterns. With the first (59), there was no scalp or brain injury; the blood in the scalp was from torn intra-osseous vessels, and there was no history of injury. Accompanying another fracture (65), there was no brain injury, but the leptomeninges on the vertex of the cerebrum were livid from traumatic bleeding. There

101. These fragments were so small that no attempt has been made to represent them in fracture 58 (fig. 8).

are, consequently, for these 2 fractures no reliable indications of where violence met the head. Limitation, or preponderance of, leptomeningeal hemorrhage and torn brain tissue to the pole of the head where there was external injury, coupled with absence of injury of the scalp at the opposite pole, are conditions associated with 4 other fractures (60, 61, 62 and 72); such brain contusions are direct, and blows to these heads were probably close to the end of the fracture nearest the damaged brain. There were signs of trauma at, or not far from, the vertex of 3 other heads (66, 71 and 76) with contrecoup bruising of the bottom of each brain, more toward the rear than usual. These were in the bodies of 3 men who fell; it seems fair to assume that the craniums were not previously freshly fractured. In 3 more heads (67, 68 and 70), the brain wounds probably were contrecoup notwithstanding absence of external injuries at the opposite pole. No information was obtained of how the injuries of 1 body (68) were sustained, but falls caused those of the others (67 and 70). This disposes of 12 of the 22 sagittal fractures: 3 with force to the top of the head and indirect bruising of the bottom of each brain with the heads in motion when injured; 4 associated with direct brain injuries and 3, with brain injuries, probably contrecoup; for 2, no assumptions are warranted. It is remarkable, but not at all astonishing, that with the other 10 fractures there were uniformly contusions of the brain at one pole of the sagittal fracture and scalp injuries at the other, or, in some instances, at both poles. In other words, the craniums were broken when their motion was checked suddenly, and fractures beginning at the pole where the blow was received coursed sagittally from that point.

When the medicolegal postmortem examinations resulting in our records of the 1,278 linear traumatic cranial fractures began in 1911, interest in satisfactory explanations of the fractures was not so acute as during subsequent years. From the onset, however, when spots of hemorrhage were seen in the deep layers of the scalp, cuts were made to learn how close to the external surface the bleeding extended. Decisions were made as to whether the blood was from torn vessels in bruised layers of the scalp or from vessels within or close to the bone torn because the bone broke. Tears in small blood vessels in the fat just beneath the corium of the scalp occur sometimes without abrasions, discolorations or other signs of trauma on the surface. In many scalps, especially those of Negroes, this adipose tissue is a thick layer and can easily accommodate considerable blood. With death soon after accidents, the blood accumulating in this fat is less and the time is too brief for its infiltration to the deep layers, where it is promptly noticed when the scalp is turned inside out in front and back flaps on the

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cranium. Appreciation of the significance of these conditions gradually increased in the course of time, so that in the latter part of the period, from 1911 to 1924, cuts from within outward were often made in the scalp at places antipodal to brain injuries when the deeper scalp layers bore no stain of blood. Naturally, in this way, some scalp contusions previously unsuspected were discovered. Applications of the principles involved also brought about detection of healed cranial fractures diametrically across from superficial *plaques jaunes* of the brain. Some of these healed fractures were barely visible, and then for only a portion of what was undoubtedly their original length and distribution. It is probable that had the methods of examination of the scalp been thorough throughout the period of thirteen and a quarter years, scalp wounds squarely across from brain injuries would have been found with more than 10 of the 22 sagittal fractures.

#### MECHANISM

In the comments on the 80 fractures in our series and their concurrent injuries there are many allusions to the way the fractures were made. Ample consideration has been given independent fractures of the orbital roofs and ventral ring fractures of the vertex. In general, for fractures with satisfactory information about wounds of the scalp, brain and other parts of the body, as well as the circumstances attending the casualties, one of the main justifiable conclusions is that the directions of the force and fracture are usually parallel. Questions of priority for any of the accepted theories of the mechanism of traumatic fractures of the cranium are difficult to settle. Theories and their discussion have already endured two thousand years. But there is unwonted accord by modern writers in giving credit to Schwartz<sup>17</sup> for establishing this conformity in the direction of force and violence. However, it is quite likely, as their investigations were published only a year apart, that while Schwartz was arriving at his decision by studies of fractures from human calamities, Félizet<sup>15</sup> was obtaining a similar inference with a hammer and chisel in experiments on human skulls. The homicidal fracture made with an ax (58 in our series) is singularly corroborative of Félizet's results. Other transverse fractures and many sagittal fractures in our series are indubitable vouchers for this agreement between violence-direction and fracture-direction.

From the place struck squarely with blunt force, fractures should radiate in all directions as meridians toward the opposite pole. All such meridians lie in planes along which violence is propelled. It is true that from some places in the vault where the thickness of the wall is fairly uniform fractures do radiate in various meridians, for-

ward, backward, down the sides or at other angles, but those passing down as transverse fractures are more numerous than fissures with an oblique or sagittal course. This is brought about by a number of factors, among which are resistance of the spine behind, the inertia of the face mass in front, the thin lateral walls and the protrusion of the base toward the center of the cranial cavity at the transverse spheno-occipital synchondrosis. Meyer<sup>102</sup> called attention to the spiral contour of the periphery of the cranium in the sagittal plane—a smooth curve up and back from the glabella and over the vertex continued as a smaller coil from the occiput down, then forward and, finally, upward in the clivus. This also promotes an excess of transverse folding of the cranial floor, so that the fractures yield front and back more than other fragments. As was pointed out in the discussion of the transverse fractures in our series, they are of two sorts: dorsal and ventral. This is well shown in the composite illustrations by Félizet<sup>103</sup> and Dulles,<sup>104</sup> in which the paths followed in the inner table of the bottom half of the cranium by many fractures are represented in single diagrams. The region of greatest exemption in the floor of the middle fossa is that formed by the large wings of the sphenoid bone. Although the bone forming them is thin and usually translucent, they are protected outside by the thick crest dividing the zygomatic and temporal fossae, and to the rear of this by the heavy ridges of the roots of origin of the zygomatic arches. On the inside of each greater wing, the pterygoid processes jut forth vertically downward from the outer surface and act as girders for the floor. Fractures cross the base in front and behind these processes, but rarely through them. Behind them, the large carotid foramina and in front, the sphenoid clefts and optic foramina, seem to act as lures for the breaks.

But violence is more commonly below the crown at or near the base level.<sup>105</sup> This vaguely defined horizontal belt in the cranial wall is quite plain in front where the junction of vault and floor approaches a right angle. Passing back, its distinctness lessens and is only faintly evident in the rounded wall where the hemispheres of the cerebellum lie. Radiation of fractures from the base level and from places just above or below this level is limited by architectonic features more profoundly than is the case with those beginning higher in the vault.

102. Meyer, G. H.: *Die Statik und Mechanik des menschlichen Knochengerüsts*, Leipzig, Wilhelm Engelmann, 1873, p. 236.

103. Félizet,<sup>15</sup> plate 1, p. 44.

104. Dulles,<sup>10b</sup> plate XXVIII, p. 337.

105. Baum, W.: *Beitrag zur Lehre von den indirekten Schädelfrakturen*, Arch. i. klin. Chir. 19:381, 1876. Rawling, L. B.: *Fractures of the Skull*, Lancet 1: 973, 1904. Walton.<sup>18</sup>



For the buttresses <sup>106</sup> running up and down from the base level hinder horizontal bending. The panels between the buttresses behave like a barrel stave does when, lying convex side up, it is jumped on; it breaks across. Fractures run vertically in the panels because the buttresses do not spread apart readily. They support the panels horizontally as the ground supports the ends of the barrel stave. With sufficient force, of course, the buttresses also break. But radiation is usually up and down in these regions, and fractures are guided by the buttresses into portions of the cranial wall between them. Although others, notably Aran <sup>12</sup> and Trélat, <sup>6b</sup> had observed the frequency of vertical fractures in the panels, Félizet's prestige for the explanation of their course has been and probably will continue to be time-honored. At this point it is expedient to add to the factors conducive to transverse radiation from the vault the greater distance between the two lateral, than between the other, buttresses.

The accounts of the 45 ring fractures in the literature are full of statements about headlong falls, and exceptionally about falls so that the bottom of the cranium was violently pushed up by the spine. These, supplemented by the experimental production of a few ring fractures made by blows on the vertex, leave the impression that basal ring fractures are due to force vertically directed from above or below. Such an impression clashes with the profusion of evidence that many of our 36 basal ring fractures were produced by violence applied at the occiput. But this apparent disagreement should not be taken seriously, because the fractures in the two series are so similar that it is fair to assume that rather uniform conditions prevailed in the entire lot of 81 basal ring fractures. There were several mechanisms. Excluding those made experimentally, the incidence of the different mechanisms in the two series, in all likelihood, was much the same. A few were due to impact of the spine, some from force directed down from the vertex and many from bumps on the back of the head. The way force alined with the spine makes these ring fractures requires no explanation.

It may be recalled that the 80 fractures represented in figures 5 to 9 were selected from the records of 1,278 linear cranial fractures due to blunt force. With a view to better understanding of the basilar ring fractures from injury of the back of the head, a cross-section

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106. In the accounts of skull fractures most textbooks give some consideration to these thicker vertical parts of the cranial wall. Trélat, <sup>6b</sup> in 1855, and subsequently Félizet, <sup>12</sup> in 1873, called them buttresses ("poutres du crâne") of Rathke. Hilton also described them. "Arcs-boutant" and "murs-boutant" are other designations (Duret <sup>96</sup>). They number 6: 1 in front and 1 behind, both in the sagittal plane: 1 on each side with the external angular process as its strongest part; a second lateral pair including the mastoid processes and petrous bones. See Le Count and Apfelbach. <sup>4a</sup>

study was made of the remaining 1,198 necropsy records to learn what sort of fractures result from blows at the occiput when ring fractures are *not* produced. The records examined numbered 352, about 30 per cent of the 1,198. They concerned necropsies made in six short periods quite evenly spaced during the thirteen and a quarter years. Of these 352 linear cranial fractures, 40 were produced by force at or near the occiput; each one of the 40 was associated with wounds of the scalp covering the lambda or the inion. Among the 40, there were 10 sagittal fractures behind the foramen magnum with more or less irregular branching at their front ends; 2 others were paramedian.<sup>107</sup> The remaining 28 of the 40 fractures were rings or segments of either large or small rings. Two were ring fractures with so much asymmetry they were not used to augment the selected 80. A third fracture was simply the back half of a large ring; another coursed horizontally in the back half of the cranium; 3 followed the lambdoid suture to the left, and 3 others to the right, from the midline. The rest of the 28, as one would expect, were fractures lengthwise the occipital panels: 8 were in the left panel and 7 in the right; and in 3 craniums both panels were split with fractures beginning at the inion. From this reckoning, 11, or 12 per cent, of the 1,278 fractures were from injury of the back of the head, and the fractures so produced were roughly one third in the midline and two thirds in rings or segments of rings.

A more interesting outcome of the survey is the conclusion that both large and small basilar symmetrical ring fractures produced by trauma at the occiput are simply part of a pattern which includes sagittal and paramedian fractures coursing forward in the base and many fractures which may be regarded as segments of rings. The suggestion has been made<sup>107</sup> that force at the occiput is transmitted directly to the top of the spine. This opinion is based on the oblique position the cranium has on the top of the spine, with the front of its floor higher than the rear and with the anterior portions of the opposed articulating surfaces of the atlas and occipital condyles markedly sloping upward and forward. Force directed obliquely against an immovable, irrefrangible object tends to ricochet at an angle equal to that of collision. Instead of driving the skull down on the spine, according to this view, force from the occiput is disposed to tear it away from the top of the spine. But the atlas is so firmly bound to the occipital bone that they do not tear apart. And so it happens that portions of one or both lateral halves of the cranial floor are broken away from the remainder by sagittal or paramedian fractures. On rare

107. Masse, E., and Cam, St. Pierre: *Étude médico-légale à propos d'une fracture du crâne par un coup du baton sur le vertex*, Ann. d'hyg. pub. et de méd. lég., series 2, 37:124, 1872.

occasions, the parts left attached to the spine are more or less symmetrical cup-shaped disks with diameters which vary widely. Most frequently, the fractures run for only long or short distances in locations where such disks have their rims. This suggestion to explain ring fractures of the base from force directed against the back of the head has some confirmation in the fracture produced experimentally by Quénu and Tesson.<sup>66</sup> Another, but quite different, fracture from violence at the occiput, made by Perrin,<sup>108</sup> is cited by many writers (fig. 10). It was made by dropping the head of the body of a young man, on a padded surface. In his comments about this fracture and about others he made, Perrin used the terms indirect and contrecoup synonymously. If the head, when dropped, was entire, as the account by Perrin implies, the question of a possible tug by the face mass when the head struck and the rôle such a force had in pulling the bones of the face away from those of the cranium is worthy of consideration.

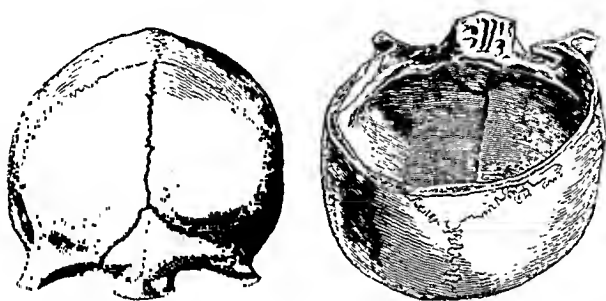


Fig. 10.—An indirect fracture made by Perrin by dropping a head on a cushioned surface so that the occiput struck first. (From Legouest, L.: *Traité de chirurgie d'armée*, Paris, 1872, p. 212.)

For many years descriptions in textbooks of the dynamics of linear cranial fractures have been based in a large measure on the experiments of Hermann,<sup>49</sup> Schranz<sup>48</sup> and Messerer,<sup>51</sup> and on the bursting and bending theories to which their investigations gave birth.<sup>50</sup> Most of their experiments were made with loose heads, or with the bottom halves of empty skulls. Practical application of the bursting and bending theories has helped to explain involved and apparently disorderly comminution, the "fractures à grand fracas" of Félizet. It has also enabled authors to differentiate the two forms of fractures in illustrations.<sup>109</sup> These descriptions of the way fractures occur, so dominated by conceptions of bursting and bending, fail to mention that the bursting theory was brought forward a decade before the

108. Perrin, M.: *Les fractures du crâne par contrecoup*, Bull. et mém. Soc. d. chir. de Paris 4:128, 1878; expériment 4, p. 132.

109. Körber.<sup>60</sup> van Nes.<sup>63</sup>

work of Hermann, by Forgues in his "fracture par éclatement,"<sup>110</sup> or that Forgues frankly stated that his explanation was not new; he gave credit for his ideas to Chassaignac.<sup>110</sup> who wrote in 1842:

Je ne pense pas que l'existence d'une fracture à une certaine distance du point frappé, suppose nécessairement une résistance inégale dans les différents points de l'étendue du crâne. La mécanique nous apprend que si l'on soumettait à une forte pression une sphère creuse, élastique, parfaitement homogène de substance et d'épaisseur, la rupture se produirait au sommet des courbes dont la courbure serait augmentée, et non pas dans les points directement soumis à la compression.

There is no clue to the source of Chassaignac's knowledge, nor is it very material whether the meridians start to burst at the equator or at the poles. There is a strong likelihood that Chassaignac's comprehension of bursting fractures was a reflection of the work of physicists with the vibrations of rings and bells.<sup>111</sup> And it is quite probable that the experiments performed by Sir Charles Bell by hitting metal rings with a hammer had a similar origin notwithstanding that they were made in 1816.<sup>27</sup>

The experiments on loose heads by Hermann and others were mainly concerned with cranial architecture and elasticity, and the relations of these to direction of the force. Neither in their experiments nor in the ensuing deductions is the influence of the weight of the trunk or structures of the face given the attention it deserves. Duret,<sup>66</sup> and his pupil Poulain,<sup>74</sup> who used entire bodies, declared that the part of the cranium receiving the blow slips away from the remainder held rigidly to the spine. Baum<sup>112</sup> insisted that the trunk often acts like a one-armed lever with its fixed point where the body is supported by the feet. We believe that the weight of the trunk and its extremities, as well as the inertia of the extracranial part of the head, should invariably be included among other factors responsible for not only the fractures but also the location and other characteristics cranial fractures possess.

#### SUMMARY

Because they were more or less symmetrical or had split the cranium to some extent in lateral halves, cranial fractures in 80 bodies are described, and explanations are offered for how they occurred. The 80 bodies were among 1,278 with traumatic, linear, cranial fractures disclosed by necropsy.

110. Chassaignac, E.: *Lésions traumatiques du crâne et des parties qu'il contient*. Thèse du concours. Paris, 1842.

111. Schroen<sup>100</sup> mentions the physicists Leibnitz, Wedel and Stosch, but does not give references.

112. Baum, W.: *Beitrag zur Lehre von den indirekten Schädelfrakturen*, Arch. f. klin. Chir. 19:381, 1876.

The mechanism of origin and other particulars of ring-shaped fractures in the cranial base in 36 of the 80 bodies are discussed together with the details reported in the literature regarding similar fractures in 45 other craniums.

An attempt is made to account for ring fractures of the base caused by violence at the occiput.

Symmetrical incomplete ring fractures ventrally placed in the vertex and obliquely directed from behind downward and forward observed in 5 craniums are reported, and suggestions are made for the way they were produced.

The usefulness of all relevant evidence in interpreting the mechanism of any traumatic, linear, cranial fracture is illustrated.

Some of the important contributions to the development of modern opinions of the dynamics of traumatic, linear, cranial fractures from blunt force are reviewed.

# BILE PERITONITIS

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It has been impossible to correlate laboratory and clinical experience in relation to bile peritonitis because of the striking contradictions in data obtained from the two sources. These contrasting data have not been understood, yet the results of laboratory experiments have been applied to the clinical problem. The results have been incomprehensible because the two methods of study are incompatible for this subject.

## CONTINUOUS EXTRAVASATION OF STERILE BILE

Recently, Wangenstein,<sup>1</sup> Horrall,<sup>2</sup> Rewbridge<sup>3</sup> and others repeated and elaborated on the experiments of earlier workers, and showed that large quantities of sterile bile poured continuously into the peritoneal cavity of an animal will produce death within from six to seventy-two hours. In most of these experiments long incisions or large apertures were cut in the gallbladder or the bile duct, and the abdomen was sutured tightly. Thus Bohn,<sup>4</sup> in 1775, removed the gallbladder in dogs without ligating the cystic duct and found that most of the dogs died. In 1902, Ehrhardt<sup>5</sup> sectioned the choledochus in 12 dogs and cats. In twenty-four hours the animals were slightly jaundiced. Within from two to six days they were intensely jaundiced, and most of them had convulsions; all of them died. In 1910, Noetzel<sup>6</sup> incised the gallbladder of 17 rabbits and closed the abdominal wall. The animals died. In 1921, Fulle<sup>7</sup> found that large incisions in the gallbladders of dogs and rabbits invariably proved fatal. Although other laboratory workers obtained

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Presented before the Surgical Section of the California State Medical Association, Del Monte, Calif., April 24, 1933.

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1. Wangenstein, O. H.: On the Significance of the Escape of Sterile Bile into the Peritoneal Cavity, *Ann. Surg.* **84**:691, 1926.

2. Horrall, O. H.: Experimental Bile Peritonitis: Its Treatment in the Dog, *Arch. Int. Med.* **43**:114 (Jan.) 1929.

3. Rewbridge, A. G.: The Etiologic Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis, *Surg., Gynec. & Obst.* **52**:205 (Feb.) 1931.

4. Bohn, quoted by Rost: *The Pathological Physiology of Surgical Diseases*, Philadelphia, P. Blakiston's Son & Co., 1923.

5. Ehrhardt, O.: Ueber Gallenresorption und Giftigkeit der Galle im Peritoneum, *Arch. f. klin. Chir.* **64**:314, 1901.

6. Noetzel, W.: Experimentelle Untersuchung zur Gallenblasen Perforations Peritonitis, *Arch. f. klin. Chir.* **93**:160, 1910.

7. Fulle, G. B. C.: Contributo sperimentale alle ferite della cistifellea e alla colemia sperimentale, *Arch. ital. di chir.* **4**:229, 1922.

diametrically opposed results, I believe that careful analyses of experimental data prove that death follows when large quantities of bile are continuously extravasated into the peritoneal cavity of the lower animals.

Every constituent of bile has been considered by various experimenters to be the cause of death in these animals, but the work of Wangensteen,<sup>1</sup> Horrall<sup>2</sup> and Ravdin, Morrison and Smyth<sup>3</sup> proves that bile salts are the only factors that can be responsible. However, it has not been proved that they, *per se*, are the sole cause of death. Numerous experiments have shown that they may be injected intravenously, in relatively large amounts, without sequelae.

Corresponding examples occurring in man are virtually unknown. In many thousands of autopsies, few, if any, comparable illustrations are afforded. Thus Robertson,<sup>4</sup> Rusk,<sup>5</sup> Conner<sup>6</sup> and Ophüls<sup>7</sup> reported that they remembered in their total experience only 1 or 2 cases in which diffuse, sterile bile peritonitis emanating from a constant outpouring of bile caused death. In a series of 377 necropsies in which I found grossly diseased gallbladders, no instances of bile peritonitis were encountered.

Surgical experience has offered a few illustrations of death following slippage of the tie of the cystic duct or severance of anomalous biliary ducts. Extremely few reports have been published relative to the frequency of this catastrophe in surgery. Personal conversations have elicited citations of only one or two instances in the memory of some of my notable confrères. Most of the cases which were recalled did not fall into the category of diffuse sterile bile peritonitis, or death from this source was not proved. When the records of remembered cases were reviewed, I found that the data were usually inadequate for critical study, or that the illustration cited was not one of sterile bile peritonitis.

Clinically also, sterile bile peritonitis seems rare and relatively innocuous.<sup>10</sup> In 1735, Wedekind<sup>11</sup> noted a case of intraperitoneal escape of bile after traumatic wounds of the liver, with recovery of the patient. In 1785, Skeete<sup>12</sup> recorded the case of a boy who fell from a tree and lacerated the gallbladder. Death did not occur until six weeks later, when the peritoneal cavity was found filled with bile-stained fluid. Paracentesis was performed on the twenty-fourth day after injury, when 16 pints (8 liters) of bile-stained transudate was removed, and at

8. Ravdin, I. S.; Morrison, M. E., and Smyth, C. M.: Bile Peritonitis and Bile Ascites, *Ann. Surg.* **89**:867, 1929.

9. Personal communication to the author.

10. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, *Surg., Gynec. & Obst.* **42**:782 (June) 1926.

11. Wedekind, A. J.: *De vulnere hepatis curato*, Jena, lit. Mullerianis, 1735.

12. Skeete, Thomas: Case of Considerable Effusion of Bile into the Cavity of the Abdomen in Consequence of a Fall; with the Appearance on Dissection and Some Additional Remarks, *London M. J.* **6**:274, 1785.

autopsy, when from 2 to 3 gallons (8 to 11 liters) of similar fluid was encountered. Fryer<sup>13</sup> reported the case of a boy, aged 13, who was struck by a wagon shaft. Two weeks later a mass appeared over the region of the gallbladder. On aspiration, 13 pints (6 liters) of bile-stained fluid was withdrawn. Twelve days later 15 pints (7 liters) was removed; nine days later, 13 pints, and twenty days later, 6 pints (3 liters). The boy recovered without further aid. In 1843, Budd<sup>14</sup> reported the case of a man who was struck in the abdomen by a heavy ladder. During the four months after his injury he was tapped eight times, and bile-stained transudate was removed. In 1845, Abraham Coles stated that in his experience not every puncture of the gallbladder was fatal. In 1882, von Pitha and Billroth<sup>15</sup> pointed out that the liver and gallbladder have frequently been punctured by saber and bayonet wounds, and that the patients have lived. In 1884, Smarth<sup>16</sup> removed a projectile from the liver. Considerable bile had oozed into the peritoneal cavity, yet the patient recovered. Petersen<sup>17</sup> aspirated 5,600 cc. of bile from the peritoneal cavity of a boy traumatically injured. Five weeks after injury two rents in the gallbladder were successfully sutured. In most saber, bayonet and projectile wounds involving the liver or gallbladder, organisms enter the peritoneal cavity. Some of the aforementioned cases were therefore not instances of sterile bile peritonitis, yet death resulted late, if at all.

In 1829, Compaignac<sup>18</sup> described the case of a man, aged 35, who received a violent blow in the abdomen. He did not die until eighteen days later, yet autopsy showed a rent in the left hepatic duct and 6 pints of deep green bile in the peritoneal cavity. In 1891, Treves<sup>19</sup> pointed out that in choledochotomies it was often necessary to insert gauze drains about the incised common duct and at the same time to drain the pouch of Douglas "abdominally or vaginally" with glass tubes to "care for the drainage of bile." Landerer<sup>20</sup> reported a case of rupture of a bile duct in which sixteen successive punctures of the abdominal cavity were

13. Fryer: Case of Extravasation of Bile into the Cavity of the Abdomen from Rupture of the Liver or Gallbladder, *Tr. Med.-Chir. Soc.*, London 4:330, 1813.

14. Budd, George: *Diseases of the Liver*, Philadelphia, Blanchard & Lea, 1853.

15. von Pitha and Billroth: *Handbuch der allgemeinen und speciellen Chirurgie*, Stuttgart, Ferdinand Enke, 1882, vol. 3, p. 190.

16. Smarth, quoted by Pantaloni, P.: *Chirurgie du foie et des voies biliaires*, Paris, Institut Bibliothèque Scientifique, 1899.

17. Petersen, W.: *Beiträge zur Pathologie und Therapie der Gallensteinkrankheit*, *Beitr. z. klin. Chir.* 23:705, 1899.

18. Compaignac, J. A. J., quoted by Terrier and Auvray.

19. Treves, Frederick: *A Manual of Operative Surgery*, Philadelphia, Lea Bros. & Co., 1892.

20. Landerer, A.: *Verletzung der Gallenwege; Gallenenerguss in die Bauchhöhle, Heilung*, *Deutsche Ztschr. f. Chir.* 29:611, 1889.



performed, with a total removal of 35 liters of bile. Garrett<sup>21</sup> removed 16 quarts (15 liters) of bile by repeated aspirations in a man traumatically injured, and twenty days after injury operation showed a tear in the posterior wall of the common duct. Recovery ensued. Uhde<sup>22</sup> removed 14.5 Kg. of bile by paracentesis twenty-three days after injury. Thirty-seven days later, 9 Kg. of bile was aspirated, and the patient recovered. Thompson<sup>23</sup> removed 4 quarts (4 liters) and later 5 quarts (5 liters) of bile and still later five or six aspirations of several quarts each were performed; and recovery ensued. Garré<sup>24</sup> reported the examination of a patient two months after injury, when a large amount of bile was evacuated from the peritoneal cavity; the patient recovered. Hildebrandt<sup>25</sup> found a large quantity of bile in the peritoneal cavity twenty-three days after injury from a tear in the hepatic duct. Ricketts<sup>26</sup> reported 28 cases of traumatic rupture of the biliary tract in which the patients had been operated on, with a mortality of 22 per cent. Meissner<sup>27</sup> found that in 25 per cent of 12 cases of traumatic rupture of the common duct and in 30 per cent of 7 cases of rupture of the hepatic duct recovery occurred. Courvoisier<sup>28</sup> collected 34 cases of rupture of the biliary tract, with 12 recoveries after surgical intervention. Amante<sup>29</sup> collected 101 cases of traumatic rupture of the biliary passages. He believed that without surgical intervention death is sooner or later inevitable. McWilliams<sup>30</sup> stated, however, that normal bile, even in large amounts, is fairly well tolerated by the peritoneum. Many of the aforementioned cases confirm McWilliams' belief, although it is

21. Garrett, R. W.: Traumatic Rupture of the Bile Duct, *Ann. Surg.* **31**:227, 1900.

22. Uhde, C. W.: Zerreiung eines Gallenganges mit glcklichem Ausgange, *Arch. f. klin. Chir.* **25**:485, 1880.

23. Thompson, J. F.: Bile in the Abdominal Cavity, *Boston M. & S. J.* **145**: 186, 1901.

24. Garré, C.: Traumatische Hepaticusruptur geheilt durch eine Hepato-Cholangio-Enterostomie, *Beitr. z. Physiol. u. Path., Festschr. L. Hermann*, 1908, p. 72; quoted by Thöle.<sup>47</sup>

25. Hildebrandt, W.: Ueber die traumatische Ruptur des Ductus hepaticus, *Arch. f. klin. Chir.* **81**:646, 1906.

26. Ricketts, B. M.: Rupture of the Gall-Bladder (Spontaneous and Traumatic; With and Without Operation); An Historical Review of 273 Cases, *St. Louis M. Rev.* **51**:108, 233, 276, 456 and 497; **52**:4 and 25, 1905.

27. Meissner: Die Zerreiungen der Gallenausfuhrungs-Gnge durch stumpfe Gewalt, *Beitr. z. klin. Chir.* **54**:204, 1907.

28. Courvoisier, L. G.: Casuistisch-statistische Beitrge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890, p. 152.

29. Amante, quoted by Kehr.<sup>33</sup>

30. McWilliams, C. A.: Acute Spontaneous Perforation of the Biliary System into the Free Peritoneal Cavity, *Ann. Surg.* **55**:235, 1912.

evident that surgical drainage is indicated. Kulenkampff,<sup>31</sup> Waugh,<sup>32</sup> Kehr,<sup>33</sup> Barling,<sup>34</sup> Garré,<sup>34</sup> Dirk,<sup>35</sup> Hildebrandt,<sup>35</sup> Fryer,<sup>13</sup> Barlow<sup>36</sup> and others have had cases of recovery after long periods of time. Although in most of the aforementioned cases large wounds were present in the gallbladder or biliary ducts, it is noted that pure bile is not described as being present in the peritoneal cavity in any instance. Adequate descriptions are not found in many of the clinical reports, and undoubtedly many of the deaths were due to secondary infection or to systemic lesions. In the carefully described cases bile-stained transudates were present. One wonders why bile alone was not found. The explanation may come from three possible sources: (1) The patient promptly died before the irritated peritoneum could exude serous material; (2) the bile became localized, i. e., encysted, (3) or an external escape for the bile was effected spontaneously or with the help of aspirations. In none of the patients who died was death proved to be due to sterile bile peritonitis. Those who lived ceased having diffuse bile peritonitis promptly, for localization of the bile occurred by adhesion encystment, or surgical drainage was effected. Obviously, then, sterile bile peritonitis has not been proved to be a cause of death in these cases or, indeed, of a serious consequence. It is possible that nature will not permit extravasated sterile bile to remain long enough in man to become serious, for it is changed into a localized form or transudation develops so rapidly that the ascites must be surgically drained. Adequate supportive treatment, of course, must be maintained.

Guibe<sup>37</sup> concluded that sterile bile in the peritoneal cavity is innocuous. McWilliams, Arth, Sick and Fraenkel,<sup>38</sup> Buchanan,<sup>39</sup> Ritter,<sup>40</sup>

31. Kulenkampff, D.: Traumatiscbe Zerreissung der grossen Gallenwege mit Ausgang in Genesung, *Zentralbl. f. Chir.* **12**:757, 1885.

32. Waugh, G. E.: Traumatic Rupture of the Common Duct in a Boy, *Brit. J. Surg.* **3**:688, 1916.

33. Kehr, Hans: Chirurgie der Gallenwege, in von Bruns: *Neue Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1913, vol. 8; Ueber einen durch ideale Cholecystotomie geheilten Fall von Schussverletzung der Gallenwege, *Zentralbl. f. Chir.* **19**:645, 1892.

34. Barling, H. G.: Case Report, *Tr. Midland M. Soc., Lancet* **1**:34, 1901.

35. Dirk: Traumatiscbe Choledochusruptur, *Zentralbl. f. Chir.* **33**:783, 1906.

36. Barlow, W. B.: Case of Tumor in Right Hypochondrium Occurring After Injury from Which a Large Quantity of Fluid Resembling Bile Was Repeatedly Withdrawn by the Operation of Tapping, *Tr. Med.-Chir. Soc. London* **27**:378, 1844.

37. Guibe, M.: Les cholépéritonites avec intégrité apparente des voies biliaires, *Rev. de chir., Paris* **49**:233, 1914.

38. Sick, C., and Fraenkel, E.: Ein Beitrag zur sogenannten galligen Peritonitis, *Beitr. z. klin. Chir.* **85**:687, 1913.

39. Buchanan, J. J.: Bile Peritonitis Without Evident Perforation of the Biliary Tract, *Surg., Gynec. & Obst.* **26**:303, 1918.

40. Ritter, C.: Die gallige Peritonitis ohne Perforation, *Arch. f. klin. Chir.* **118**:54, 1921.

Burckhardt,<sup>41</sup> Hearn,<sup>42</sup> Terrier and Auvray<sup>43</sup> agreed. Gibbon,<sup>44</sup> and, later, Schlatter,<sup>45</sup> found that sterile bile was innocuous in the peritoneal cavity unless absorbed in large amounts. Courvoisier concluded from studies of animals and from clinical experiments that sterile bile in the peritoneal cavity is innocuous even in relatively large amounts. Hermes<sup>46</sup> came to similar conclusions after an experience with a case of extensive bile peritonitis in man due to traumatic perforation of the common duct. Lewerenz<sup>47</sup> reported the case of a boy, aged 2½ years, who suffered a traumatic rupture of the common duct and recovered after operation. Lewerenz collected 63 more cases from the literature, many with recovery. When death occurred, he attributed it to the absorption of biliary salts. Ritter and Burckhardt insisted that death from cholemia following rupture of the bile ducts has never been observed. Stierlin<sup>48</sup> stated that sterile bile contained within the peritoneal cavity for long periods produced death by fatal toxemia. Malnutrition invariably occurred, however, and studies at autopsy indicated that death was due to metabolic disturbances. It has not been demonstrated that encysted bile is absorbed in man in sufficiently large quantities to cause toxemia. Ricketts reported 273 cases of spontaneous and traumatic perforations of the extrahepatic tree; he found a decidedly better outcome in the cases of trauma (i. e., sterile bile). Thöle<sup>49</sup> also came to the same conclusion (see addenda).

During the last twelve years I have had only one case of diffuse sterile (?) bile peritonitis at the San Francisco Hospital:

A woman, aged 45, had had moderately severe attacks of gallstone colic for one year. Seven days before admission to the hospital she had a severe pain followed by vomiting, with localized tenderness and rigidity over the gallbladder. It was believed that she had moderately acute cholecystitis, but as the temperature was normal and the white cell count 9,250, she was treated conservatively. Observation continued for five days, during which time the four hourly temperature readings remained normal and the white count stayed below 9,000. The patient was not

41. Burckhardt, H.: Perforationslose Gallenperitonitis, *Beitr. z. klin. Chir.* **128**:209, 1932.

42. Hearn, W. J., in discussion on Jopson: Rupture of the Gallbladder with Profound Toxemia, *Ann. Surg.* **40**:424, 1904.

43. Terrier, F., and Auvray, M.: Les traumatismes du foie et des voies biliaires, *Rev. de chir., Paris* **17**:16, 1897.

44. Gibbon, J. H., in discussion of paper by Jopson.<sup>42</sup>

45. Schlatter, C.: Die Behandlung der traumatischen Leberverletzungen, *Beitr. z. klin. Chir.* **15**:531, 1896.

46. Hermes: Case Report, *Ann. Surg.* **16**:393, 1892.

47. Lewerenz: Ueber die subcutanen Ruptur der Gallenwege traumatischen Ursprungs, nebst einem casuistischen Beitrag, *Arch. f. klin. Chir.* **71**:111, 1903.

48. Stierlin, R.: Traumatische subcutane Ruptur des Ductus choledochus, *Deutsche Ztschr. f. Chir.* **73**:462, 1904.

49. Thöle, F.: Die Verletzungen der Leber und der Gallenwege, in von Bruns: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1912, vol. 4, p. 144.

jaundiced, but because of persistent abdominal tenderness and rigidity, exploration was undertaken. Large pools of bile were found in the peritoneal cavity. Unfortunately cultures were not taken. The gallbladder was perforated and empty except for two mulberry stones, which were removed. A cholecystostomy was performed, and the patient had an uneventful convalescence.

#### SINGLE LARGE EXTRAVASATION OF BILE

Many authors have showed that large quantities of sterile bile may be poured experimentally into the peritoneal cavity at one time without the occurrence of death. Thus, Malpighi<sup>50</sup> in 1666, made a biliary fistula in a dog and noted that large quantities of bile might be spilled without serious consequences. In 1839, Thomson<sup>51</sup> stated, "In experiments on animals it has been proved that rupture of the gallbladder does not necessarily cause death. These experiments seem to warrant the conclusion that it is not so much the original escape of fluid that causes death as it is the continual seepage of bile into the peritoneal cavity." In 1767, Herlin<sup>52</sup> incised the gallbladders of cats after ligating the cystic duct, thus allowing the bile from the gallbladder to empty into the peritoneal cavity. He then sewed the gallbladder wound together, and the animals lived. At autopsy, several weeks later, no trace of bile was found in the peritoneal cavity, and the gallbladder was filled with a colorless fluid. L'Anglais repeated the experiment on 2 dogs, but he also removed the gallbladder. The dogs lived. Fulle found that small incisions left open in the gallbladder or bile ducts did not prove fatal. Later, examinations at autopsy showed that these small wounds had closed. Noetzel concluded from experiments on dogs that the contents of the gallbladder, when allowed to drain into the peritoneal cavity, produce no untoward results. Bostroem,<sup>53</sup> Emmert,<sup>54</sup> Hering,<sup>54</sup> Villaderbo,<sup>54</sup> Compaignac,<sup>54</sup> Ammusat<sup>54</sup> and Schwartz<sup>54</sup> performed similar experiments with similar results. Wangenstein<sup>1</sup> and Horrall<sup>2</sup> recently repeated the experiments, showing that the sterile contents of the gallbladder may be emptied into the peritoneal cavity with impunity. The peritoneum remains smooth and glistening.

Clinically, single large extravasations of sterile bile into the peritoneal cavity are extremely rare. It is only following trauma that sterile bile is evacuated from the gallbladder into the peritoneal cavity. But even in these cases a constant stream of bile may be poured into the peritoneal cavity through the aperture in the gallbladder wall via the cystic duct.

50. Malpighi, quoted by Budd.<sup>14</sup>

51. Thomson, William: *Diseases of the Liver and Bile Passages*, New York, E. Barrington & George D. Haswell, 1842.

52. Herlin, quoted by Thomson.<sup>51</sup>

53. Bostroem, quoted by Lesser, in discussion of Thiersch: *Zerreißung eines Gallenganges mit tödlichem Ausgange*, Verhandl. d. deutsch. Gesellsch. f. Chir. 8:117, 1897.

54. Quoted by Terrier and Auvray.<sup>43</sup>

It is extremely difficult to conceive of a pathologic condition in which, although the cystic duct is obstructed and the gallbladder wall and the gallbladder bile are sterile, a perforation of the gallbladder nevertheless occurs. Theoretically it is possible, but I have not been able to find a record of it. When clear bile is emptied from the gallbladder following an acute or subacute spontaneous perforation, the bile cannot be considered sterile, even though one or two swabs are taken from the peritoneum for culture. Perforations of this nature presuppose infection of the gallbladder wall, and when the wall is ruptured organisms are presumably scattered into the adjacent peritoneal areas. It is difficult to obtain cultures of organisms from single samples of bile from the gallbladder. Frequently only one of several swabs will yield a positive culture, even under these ideal circumstances. It is therefore likely that one or two samples taken from the peritoneum will yield no growth. Under these circumstances one is not justified in concluding that the extravasated bile is sterile. Much less may one overlook the site of infection at the perforation in the gallbladder wall. It is a common experience in the operating room, however, to note the spilling of small quantities of gallbladder or hepatic bile. Even when large quantities of bile escape during operations on the gallbladder, postoperative complications are rarely encountered. This may be due to a fear inherent in the surgeon's mind that leakage of bile will occur, for such areas are usually drained. However, in the vast majority of patients, extravasated bile is rapidly walled off by adhesions. When spilled bile is infected, drainage should be provided, but I have occasionally closed the abdomen tight without ill consequences even in cases of this sort.

#### INJECTIONS OF LARGE QUANTITIES OF BILE

Conflicting results have been obtained in the laboratory when large quantities of sterile bile were injected experimentally through the abdominal wall. Fraenkel and Krause<sup>55</sup> injected bile in varying quantities into the peritoneal cavity of guinea-pigs and dogs and found that it was well tolerated. Fulle noted that small quantities of bile from the gallbladder, when injected intraperitoneally, caused no reaction, but that large amounts proved fatal to dogs and rabbits. McWilliams found that large quantities injected into the abdominal cavity caused little trouble. Wangenstein made injections of sterile bile from the gallbladder into 3 rabbits. All of them died within five days, and all except 1 of 12 guinea-pigs died within twelve hours. The chief symptoms were lethargy, anorexia, diarrhea, rapid respiration and jaundice. At autopsy the peritoneal cavity was normal except for areas of necrosis in the liver where bile came into contact with Glisson's capsule. The kidneys showed acute nephritis, and the cortical cells of the suprarenal

55. Fraenkel, E., and Krause, P.: *Bakteriologisches und Experimentelles über die Galle*, Ztschr. f. Hyg. u. Infektionskr. 32:97, 1899.

glands were markedly degenerated. Beyond a certain quantity, additional injections of bile caused no increased reaction or rapidity of death, nor did the reactions caused by bile from the liver and gallbladder differ. Horrall claimed that when large quantities of sterile bile were continuously emptied into the peritoneal cavity of animals death ensued from a toxemia produced by the absorption of bile salts. Rewbridge repeated Wangensteen's and Horrall's experiments, but found that the peritoneum, instead of remaining grossly normal in appearance, was fiery red and covered with fibrinous exudate. Moreover, he constantly obtained positive cultures of *Bacillus Welchii*. He was not able to find sufficient bile salts in the blood to cause death. Even when large quantities of bile salts were introduced into the peritoneal cavity, no significant rise in the bile salts of the blood was found.

Thus the laboratory has furnished three groups of conflicting evidence: 1. Many workers have found that large quantities of sterile bile drained or injected into the peritoneal cavity were entirely innocuous. Bacteriologic cultures were uniformly negative. 2. Others observed death within from six to one hundred and twenty hours after similar experiments without evidence of peritoneal reaction or infection, but with marked changes in the kidneys and suprarenal glands. They held that bile salts are absorbed and are toxic. 3. Rewbridge found, after similar experiments, an extensive inflammation of the peritoneum with positive cultures of anaerobes (*B. Welchii*) almost as a routine. He concluded, as did Dorsey,<sup>56</sup> in 1818, and Thomson,<sup>51</sup> in 1839, that bile salts react on the intestinal walls, making them permeable and thus permitting the escape of bacteria from the intestinal lumen. In 1931, Meleney, Harvey and Jern<sup>57</sup> expressed the opinion that after a seepage of bile had occurred, peritonitis developed secondarily from organisms which had permeated the intestine.

These three groups of conflicting results from laboratory workers seem difficult to correlate. Some assistance, however, is afforded by other experimental evidence. In 1797, Eaglesfield Smith<sup>55</sup> immersed flesh in bile for fourteen hours at body temperature and found that it lost half its weight. From this evidence he concluded that bile was a digestant of tissue. In 1866, Leyden<sup>58</sup> noted that bile acids caused a degeneration of the musculature of the blood vessel walls. Several observations have been made of edema and even of necrosis of the muscles of the abdominal wall in patients with extensive bile peritonitis.

56. Dorsey, J. S.: *Elements of Surgery*, Philadelphia, E. and R. Parker and B. Warner, 1818, vol. 1; quoted by Budd.<sup>14</sup>

57. Meleney, F. L.; Harvey, H. D., and Jern, H. Z.: *Peritonitis: I. Correlation of the Bacteriology of the Peritoneal Exudate and the Clinical Course of the Disease in One Hundred and Six Cases of Peritonitis*, Arch. Surg. 22:1 (Jan.) 1931.

58. Quoted by Legg, J. W.: *Bile, Jaundice and Bilious Diseases*, New York, D. Appleton & Company, 1880.

In 1874, Fleischle<sup>58</sup> tied the common duct of dogs and connected the liver end to the thoracic duct by means of a cannula. Though an abundance of bile acids were recovered from the lymph ducts, none was obtained from the blood stream, indicating that they were destroyed by the blood or were too greatly diluted to be recoverable. In 1931, Rewbridge was likewise unable to detect increased amounts of bile acids in the circulating blood of animals dying from extensive bile peritonitis. He therefore concluded that circulating bile acids could not be the cause of the toxemia.

If, then, extensive sterile bile peritonitis is so rare in man, how can one correlate the findings of the laboratory relative to its seriousness? Should one not expect the condition in man to be present frequently and to be the cause of death? Probably the laboratory itself has answered these questions, for Brand<sup>59</sup> showed that dog's bile contains eight times as much taurocholic acid as glycocholic acid, while human bile contains only from one-fifth to one-eighth as much. Furthermore, taurocholic acid is from twelve to twenty times as toxic as glycocholic acid. Therefore bile peritonitis in a dog is at least forty times as dangerous as a proportionate amount of bile peritonitis in man. In rabbits and guinea-pigs a similar, though less marked, disparity is found, yet from such experiments conclusions are drawn and appropriated to man. I believe that the laboratory animal itself is responsible for many of the divergent opinions which have arisen relative to experimental bile peritonitis. Meyer,<sup>60</sup> director of the Hooper Foundation, informed me that the livers of most dogs, rabbits and guinea-pigs are constantly filled with organisms. Animals used for experiments on bile peritonitis are frequently not satisfactory, even when raised and fed under strictly aseptic conditions. The liver is a virtual incubator for organisms, and it is common experience to culture aerobes, as well as anaerobes, from the bile of animals which have arrived at the experimental laboratory through the usual channels.

#### ENCYSTED BILE

In 1823, Cooper<sup>61</sup> quoted a case of Calacin's in which a large extravasation of bile was limited by adhesions, and the patient recovered. Labrosse<sup>62</sup> reported a case of a boy aged 17, who fell from a ladder onto a wall, striking the right hypochondrium. Eight or ten days later the patient's abdomen began to swell and continued protruberant for two years, when Jaboulay operated on him. Ten liters of bile was found

59. Brand, J.: Beitrag zur Kenntnis der menschlichen Galle, Arch. f. d. ges. Physiol. 90:491, 1902.

60. Meyer, Karl: Personal communication to the author.

61. Cooper, Samuel: A Dictionary of Practical Surgery, New York, Collins & Hannay, 1823.

62. Labrosse: Contribution à la étude du cholépéritone spontané, Thèse de Lyon, no. 86, 1912.

encysted about the gallbladder, which had a small patent opening that had evidently persisted for two years. In 1925, Polya<sup>63</sup> reported a case in which jaundice, clay-colored stools, an enlarged liver and fever developed seven days after cholecystectomy. Eight months later the patient was operated on again, and a cyst containing at least 200 cc. of pure bile was found at the operative site. Similar cases of prolonged encystment of bile were reported by Drysdale,<sup>64</sup> Thiersch<sup>65</sup> and Rätjen.<sup>66</sup> Certainly it is known that bile may remain encysted for long periods without serious sequelae.<sup>67</sup> Enderlin and Justin<sup>68</sup> showed that lacerations in the gallbladder wall close rapidly. Therefore diffuse extravasations of bile are prevented. Furthermore, the pressure of bile secretion is low, and this fact, coupled with the readiness of visceral and omental adhesions, permits the rapid closure of wounds in the gallbladder wall and the ready development of encystment. Recently I drained 600 cc. of infected bile which had localized about the subhepatic area when a T-tube leaked following choledochostomy. The accumulation of infected bile appeared as a mass at the operative site six days postoperatively without other clinical evidence of its development, and in spite of adequate drainage through the T-tube. Two Penrose drains leading to the site of the operation also failed to drain away the bile thus accumulated. For seven weeks postoperatively a large pool of bile (approximately 450 cc.) remained localized in this area without serious sequelae. When it was drained by a third operation, convalescence was uneventful.

#### INFECTED BILE

Infected bile which has spread diffusely through the peritoneal cavity is recognized by most authorities as being extremely dangerous. Although bile is considered by most bacteriologists to be an inhibitor of bacterial growth, bile and pus, when emptied into the peritoneal cavity of man, seem to increase the virulence of pyogenic peritonitis. Numerous cases of acute ulcerative perforations of the gallbladder and bile ducts in which large quantities of infected bile were widely dis-

63. Polya, E.: Gallencyste nach idealer Cholecystektomie, *Zentralbl. f. Chir.* 52:2341, 1925.

64. Drysdale, T. M.: Case of Rupture of the Common Duct of Liver: Formation of Cyst Containing Bile. Death Occurring on Fifty-Third Day, *Am. J. M. Sc.* 41:399, 1861.

65. Thiersch, K.: Zerreiung eines Gallenganges mit tdlichem Ausgange, *Verhandl. d. deutsch. Gessellsch. f. Chir.* 8:117, 1879.

66. Rätjen: Ueber einen Fall von traumatischer Gallencyste, *Deutsche med. Wchnschr.* 13:155, 1887.

67. Mentzer, S. H.: Acute Cholecystitis: Its Surgical Treatment, *California & West. Med.* 32:224 (April) 1930.

68. Enderlin and Justin: Ueber die Heilung von Wunden der Gallenblase und die Deckung von Defecten der Gallenblase durch transplantiertes Netz, *Deutsche Ztschr. f. Chir.* 61:235, 1901.



seminated throughout the peritoneal cavity have resulted in mortalities of from 48 to 100 per cent, depending on whether or not operative aid was immediate.<sup>69</sup> The abundant literature relative to acute cholecystic perforations during typhoid fever and parasitic infections attests to almost uniform fatality in infected, diffuse bile peritonitis unless surgical aid intervenes.

In 1757, Boerhaave<sup>70</sup> recorded the case of a man whose gallbladder was run through by a sword, and who died in three days, "convulsed." Watson<sup>71</sup> reported the case of a man whose gallbladder was perforated by a bayonet wound and who died within thirty-six hours. In 1812, Sabatier<sup>72</sup> expressed the opinion that extravasated, infected bile is absolutely fatal. In 1818, Dorsey concluded that wounds of the gallbladder are fatal because the extravasated bile irritates or disturbs the function of the peritoneum. In 1839, Thomson pointed out that perforation of the gallbladder, with infected bile, is "absolutely fatal" unless operation is performed.

In 1903, Erdmann<sup>73</sup> reported 33 instances of spontaneous rupture of the gallbladder occurring in typhoid fever. Twenty-seven of the patients were not operated on, and all of these died. Of 7 who were operated on, 4 recovered. During the past twenty years at the San Francisco Hospital only 1 case of perforation of the gallbladder has occurred in association with typhoid fever:

A Filipino boy, aged 20, was admitted to the hospital with a diagnosis of typhoid fever. His temperature ranged from 101 to 105 F. during a three week period, and he was critically ill. There followed a quiescent period of two weeks, during which the temperature ranged from 99 to 100 F. Then, over a four week period, a series of attacks characterized by chill, sudden rise in temperature and absence of pain began. Finally a severe pain about the umbilicus, with high temperature, rapid pulse and severe chill, developed. An acute condition of the abdomen was recognized and the patient was operated on within twenty-four hours. A perforated gallbladder with extensive bile peritonitis, yielding a culture of *Bacillus typhosus*, was encountered. One gallstone was found and removed, and the gallbladder was drained. The patient had an uneventful convalescence. The drain was removed on the fourth day, and no bile exuded from the wound thereafter. The contents of the gallbladder obviously emptied into the peritoneal cavity, and no further spilling occurred.

In 1890, Courvoisier<sup>28</sup> collected 34 instances of rupture of the biliary passages following trauma in which 22 of the patients died and 12

69. Mentzer, S. H.: The Acute Gallbladder Manifesting Few Signs or Symptoms, *Surg., Gynec. & Obst.* 55:716 (Dec.) 1932.

70. Boerhaave, H.: *Causus et signis acutorum, et diuturnorum morborum*, Lugduni Batavorum, J. Vander, 1735.

71. Watson, quoted by Thomson.<sup>51</sup>

72. Sabatier, quoted by Cooper.<sup>61</sup>

73. Erdmann, J. F.: Primary Typhoidal Perforation of the Gallbladder, *Ann. Surg.* 37:878, 1903.

recovered. None recovered without operation or puncture. Only 5 patients died within twenty-four hours, and the sixth died within forty-eight hours. Hemorrhage from the liver was present in 3 cases. In 1905, Ricketts recorded 273 cases of spontaneous or traumatic ruptures of the biliary tract, 224 of which were instances of perforation of the gallbladder alone. Sixty-four patients were operated on; 43 recovered, and 21 died. One hundred and sixty were not operated on; 6 recovered, and 154 died. Therefore, 67 per cent recovered following surgical treatment, while only 3.7 per cent recovered without surgical treatment. Of the 6 patients who recovered without operation none apparently had intraperitoneal drainage of bile. In Ricketts' 49 cases of traumatic rupture of the gallbladder, 29 of the patients were operated on; of these 22 recovered, and 7 died. Of the 20 patients who were not operated on, only 4 recovered, while 16 died. The cause of death as demonstrated by necropsy was purulent peritonitis. In 2 of the 4 patients who recovered without operation, the establishment of a fistula prevented death. In the third no evidence of intraperitoneal drainage was present. In 1912, McWilliams reported 108 cases of spontaneous perforation of infected biliary tracts. Even though these patients received surgical treatment, the mortality was 48 per cent. In 1918, Buchanan<sup>72</sup> collected 17 cases of rupture of the gallbladder with a mortality of 9 of the 17. Twelve of the 14 patients whose cases were complicated by infection were treated surgically, with a mortality of 50 per cent. The patients who were not operated on died. In 8 cases the duration of symptoms varied from one to six days, with a mortality of 50 per cent, and in 5 cases the duration varied from seven to twenty-seven days, with a mortality of 80 per cent.

During the past twelve years 24 cases of perforated gallbladder have occurred at the San Francisco Hospital. In 8 cases infected bile spread into the peritoneal cavity (table). In 16 cases pus alone exuded. In no instance was sterile bile found in the peritoneal cavity. The 4 patients who were not operated on died. Six of the 20 who were operated on died. One of these lived for fourteen days, until extensive pyogenic peritonitis proved lethal. Three patients died within three days from pyogenic peritonitis which was already present at the time of operation. Two died from shock within twelve hours after surgical intervention.

The careful studies of Billings and Walkling<sup>74</sup> show that most patients who have received stab or gunshot wounds of the biliary system die of hemorrhage or pyogenic peritonitis. Bile peritonitis rarely arises from injuries of this sort. Of 13 patients who had received stab wounds of the liver, 10 were operated on, and hemorrhage was found in all. Death occurred in 7 cases. In only 1 instance was bile extravasated.

74. Billings, A. E., and Walkling, A.: Penetrating Wounds of the Abdomen, *Ann. Surg.* 94:1018 (Dec.) 1931.

Death occurred in this case from pneumonia. One patient had a stab wound of the gallbladder. Hemorrhage and bile exuded, but the patient recovered after surgical intervention. Forty-two instances of gunshot wounds of the liver occurred. All of the patients had hemorrhage at operation, and 20 died. Two also had bile extravasations; 1 of these recovered, and the other died of hemorrhage. One patient with a gunshot wound of the gallbladder was operated on but died of hemorrhage. One died of hemorrhage before an operation could be performed. No operation was performed in 5 cases of gunshot wound of the liver, and all of the patients died of hemorrhage.

*Data on Eight Patients with a Perforated Gallbladder*

Hospital Number	Days in Hospital	Temperature, F.	Blood Count*	Pathologic Data	Operation and Results
D 96893	5	98.6 for 5 days	9,250 86	Large pools of bile free in peritoneal cavity; no pus, but two stones	Cholecystostomy; recovered
D 28549	12	98.6-100	16,000- 18,000 89	Gangrenous gallbladder with numerous perforations; 500 cc. of bile-stained pus; stone the size of pigeon's egg in common duct	Cholecystectomy; T-tube in common duct; recovered
D 50434	Few hours	99	17,000 92	Perforated gangrenous gallbladder with large collection of walled-off bile; one stone in common duct	Cholecystectomy; died on 14th day of peritonitis
D 56929	19	99.8-104	12,000 83	Perforation with clear bile diffuse in peritoneal cavity, purulent drainage following; no stones	Drainage of area only; recovered
D 68430	1	98.6	Not done	Perforated with bile in peritoneal cavity	Drainage of area only; died of shock on same day
D 18980	2	99-102	18,400 88	Acute friable hydrops; bile-stained peritoneum; one stone the size of golf ball	Cholecystostomy; recovered
D 40509	10 hours	98.8	11,200 80	Gangrene and perforation, bile in peritoneal cavity; no stones	Cholecystostomy; died same day
D 28594	12	98	18,000 89	Several perforations; bile and pus in peritoneal cavity; stones in gallbladder and common duct	Cholecystectomy and choledochostomy; recovered

\* White blood cells and polymorphonuclears (per cent).

The conclusion is inevitably drawn that infected bile which has spread into the peritoneal cavity is extremely serious. Most of the aforementioned cases were instances of peritonitis arising from perforations from which frank pus exuded. Only a few were instances of discharge of purulent bile. The patients obviously died of pyogenic peritonitis. The possibility of pyogenic peritonitis arising in man from digestion of the intestinal musculature by extravasated sterile bile cannot be seriously entertained. I have not been able to find a case which might be used as an illustration of this thesis. Furthermore, the marked contrast in the bile salt content of human and animal bile and the absence of anaerobic cultures in man when bile peritonitis is present must be remembered.

When bile peritonitis is suspected to be the cause of death in man, careful examinations have usually revealed pyogenic peritonitis rather than bile peritonitis. The peritoneum may be stained with bile, but the latter is only a contaminant. In many cases of suspected bile peritonitis the patients have died of hemorrhage, as Billings and Walkling<sup>74</sup> showed. And finally, the extreme rarity in man of diffuse, sterile bile peritonitis must cast doubt on its actual occurrence, for the possibilities of its presence are generously abundant.

I have been unable to find on record in the department for pathology of the San Francisco Hospital a case in which sterile, diffuse bile peritonitis was the cause of death.

#### CONCLUSIONS

1. Experiments show that bile peritonitis in animals is not comparable to that in man.
2. Diffuse, sterile bile peritonitis has rarely, if ever, been found as the cause of death in man.
3. Extravasated sterile bile is rapidly encysted in man and then becomes relatively innocuous.
4. If the bile is not encysted it provokes ascites, which soon invites surgical intervention.
5. Infected bile which has spread diffusely over the peritoneal cavity proves fatal unless promptly drained by surgical measures. Death ensues from pyogenic rather than chemical peritonitis.

#### ADDENDA

Since writing this article I have seen an excellent illustration of my thesis at an autopsy performed by Dr. D. A. Wood.

A man, aged 61, who had been drinking heavily, fell, striking the abdomen on the edge of a table. He vomited persistently for one day and then became very ill. He entered the hospital twenty hours later. The temperature was 99.4 F., and the white blood cells numbered 15,400. The abdomen was distended, rigid and tender, particularly to the right of and above the umbilicus. The patient refused to undergo an exploratory operation and died six days after the trauma.

At autopsy, 2,000 cc. of thin, syrupy, yellowish-brown fluid resembling bile was found in the peritoneal cavity. The peritoneum had a greenish tint, and the loops of jejunum were moderately distended and had a slight deposition of fibrin in a few places. The gallbladder had a large tear in its proximal third, from which normal bile was recovered. There was no evidence of gross cholecystic disease.

Advanced bilateral bronchopneumonia accounted for the patient's death. Microscopic examination showed that the kidneys and the suprarenal glands were essentially normal. The liver showed moderately advanced cirrhosis, and the wall of the gallbladder was essentially normal. Bacteriologic examination of the peritoneum showed nonhemolytic streptococci, *Staphylococcus albus* and *Bacillus coli*.

# I. THERAPEUTIC USE OF BACTERIOPHAGES AGAINST THE COLON BACILLUS

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The preparation and use of bacteriophages against the colon bacilli present special problems. The difficulties appear to be due in part to the numerous varieties and strains of bacteria included within this group and in part to the long continued association between the colon bacilli and various lytic agents of the bacteriophage group in the intestines of man and other vertebrates. A great variety of possibilities is thus presented.

Furthermore, the location of the pathologic condition in the patient may introduce additional complicating circumstances. The infectious process may be located on a surface in contact with abundant other bacteria, as in intestinal ulcer, or in contact with a more or less irritating or toxic liquid, such as the urine, in a wound or in the interior of the blood vessels. The special conditions present at the site of the infection may require careful consideration and sometimes modification in order to permit success. These regional factors are, however, of secondary importance. The primary problem is that of combat against a specific bacterial parasite which is causing the infectious disease. The specific bacteriologic diagnosis is paramount, a point sometimes neglected in the modern enthusiasm for regional specialization in medicine and surgery.

Continued study of bacteriophages discloses the complexity of this group of entities and differences in character of the various lytic agents. Those which act against the colon bacilli present peculiar problems. In preparing for laboratory service in this field one should first collect a large number of bacteriophage races from various sources. These may be obtained from samples of sewage as well as from individual samples of intestinal contents. It is also easy to get them by transfer from other laboratories which may already possess multiple races in their collections. Probably many of these races are not pure but represent mixtures of

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These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

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lytic agents associated together. These bacteriophage races are tested against various culture strains of bacteria, and when lysis of the bacteria takes place one carries out serial filtration and inoculation of the filtrate into cultures of the particular susceptible bacterial strain in order to enhance the activity of the bacteriophage to maximum potency. Then this filtrate of enhanced potency is tested against many other bacterial strains to gain an idea of its polyvalence. In practice, one then combines several of the most potent and most polyvalent filtrates for use as a stock polyvalent colon bacteriophage. The individual bacteriophage races are, however, preserved. They keep well in sealed ampules in the refrigerator. In general, the procedure of serial filtration and inoculation of successive cultures results in increased potency of the bacteriophage not only for the individual bacterial strain employed but for other strains. There are, however, exceptions to this. Sometimes the potency diminishes and eventually disappears in serial filtration experiments, and sometimes as the potency increases for one bacterial strain it becomes diminished for another. The assumption that the original bacteriophage actually represents a mixture finds support in such experiences, but one can hardly pretend that the matter is fully understood.

The idea of therapeutic use of the colon bacteriophage comes into consideration when it is recognized that the patient has ulceration of the intestinal mucous membrane, where the presence of colon bacilli may be presumed, or when cultures of the body fluids, such as the urine or blood, or cultures of wound exudate reveal the presence of colon bacilli in these specimens. The first step in the laboratory is the isolation and recognition of the bacterial parasite. Only under conditions of exceptional urgency is one justified in employing a mixed stock colon bacteriophage in treatment before there has been time for specific testing of the bacteriophage against the specific strain in the laboratory. Fortunately, in most instances the condition of the patient does not require immediate emergency use of bacteriophage in infections with organisms of this group. One therefore isolates the bacterial organism in pure culture, tests its various cultural and serologic characteristics and at the same time subjects it to serial filtration studies, at first with the mixed potent colon bacteriophage and subsequently, if necessary, with several of the individual potent races of bacteriophage, in the hope of obtaining complete lysis and, by filtration of such lysed cultures, an autogenous strain-specific bacteriophage of high potency. In desperate cases this work is pushed by continuous twenty-four hour service in the laboratory, especially in those urgent cases in which the treatment has been initiated at once with the stock bacteriophage.

Bacteriophage therapy requires not only skilful, diligent and prompt action in the laboratory but a certain understanding on the part of the physician at the bedside of the behavior of this group of agents and

the conditions for their successful use. Possession of a keen scalpel is not the only requirement for success as a surgeon. Yet one sometimes finds the physician or surgeon fully satisfied with his preparation for bacteriophage treatment as soon as he has read some commercial advertising and has obtained a supply of filtrate from the laboratory. This not only leads to unfortunate results for the patient but tends to discredit bacteriophage therapy in general. The methods of clinical application are still in the process of being perfected, but certain principles are well established. These should not be lightly regarded. Furthermore, the progress of the case needs to be checked by frequent bacteriologic study of specimens from the infected region. Intimate and sympathetic cooperation between the clinician and the bacteriologist is therefore of great importance.

Effective action of the bacteriophage on the microbes cannot be expected unless it comes into direct relation with them. When the infected region is easily reached without risk of damage to the tissues, it is best to place the bacteriophage in or on the lesion. When the infected site cannot be directly approached with safety, intravenous use of the bacteriophage, so that this agent may reach the infected tissues through the blood stream, should be carefully considered. The probable difficulties and dangers of different methods of application should be thoughtfully weighed in the light of experience in the use of bacteriophages. Intravenous bacteriophage therapy requires a special sort of bacteriophage preparation. In our experience a sterile filtrate of a lysed culture grown in protein-free asparagine medium is the most satisfactory type of preparation for this purpose.

When one has to deal with an infection of the urinary tract, in which the colon bacilli are present in the urine within the lumens of the bladder, ureter and renal pelvis and have penetrated into the lymph spaces beneath the epithelial lining of these structures, particularly that of the renal pelvis, and have ascended more or less along the collecting ducts into the medulla or even into the cortical substance of the kidney or may even have established themselves in the blood stream, the problem is not simple. The most dangerous inflammatory lesions in such a case can be reached only through the blood stream, and it is best to begin the use of the bacteriophage by intravenous administration. However, when the infection of the renal tissues has been overcome, one will find new difficulties confronting one in attempting to eradicate the bacteria from the urine in the lumens of the renal pelvis, ureter and bladder. If the urine is markedly acid or alkaline, the colon bacilli in it are able to resist even the most potent bacteriophage. This has been clearly demonstrated by experiments in the test tube in which human urine adjusted to various degrees of acidity and alkalinity from pH 5 to 8 was employed as the

culture medium.<sup>1</sup> Only in those tubes in the intermediate pH range, from about 6.6 to 7.2, was the bacteriophage able to exhibit its full lytic power. Obviously, therefore, one cannot expect bacteriophage lysis to occur in urine within the body if the chemical reaction of this medium is far from the neutral point. Fortunately, the importance of regulating the hydrogen ion concentration of the urine in pyelitis had been recognized as a result of clinical experience before bacteriophage therapy came into the field. In fact, there is good reason to believe that the usual defensive agents of the body, such as the white blood cells and the antibacterial substances of the blood plasma and the lymph, find themselves seriously at a disadvantage in a medium which is very acid or very alkaline. The urine may be made almost neutral in reaction and may be maintained in this condition by the ingestion of a fairly uniform diet, large amounts of fluid and the precisely necessary amounts of alkali-residue drugs, such as potassium citrate or the more powerful and more dangerous sodium bicarbonate, or of acid-residue drugs, such as acid phosphates or ammonium chloride. Determination of the hydrogen ion concentration of the freshly passed urine, each morning and evening, by use of phenol red, bromcresol purple and suitable comparators is the necessary guide to these adjustments, which, moreover, should be made gradually.

As a general rule, chemical antiseptics should not be used in conjunction with bacteriophages, as the lytic agent is inhibited by very minute quantities of such agents as formaldehyde, in fact by quantities too minute to exert evident effect on the bacteria.<sup>1</sup>

It has also been shown that the admixture of blood, blood serum or purulent exudate<sup>2</sup> with urine tends to interfere with the action of the bacteriophage, and it appears that mucus may act in a similar way. Local trauma to the urinary tract by instrumentation may therefore be expected to favor the bacteria as against the bacteriophage. This should receive due consideration before urologic instrumentation is undertaken.

Another matter to be thought about before introducing instruments into the ureters or renal pelves is the danger of spreading the infection to previously uninvolved locations. It is an honored surgical principle that one should not incise through an infected region into a region free from infection. For example, the experienced abdominal surgeon does not open the peritoneal cavity by an incision passing through a furuncle of the abdominal wall. When, therefore, one is certain that the bladder urine is infected with colon bacilli, it is well to pause for consideration before passing an instrument through this bacterial culture into a possibly

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1. Frisbee, Frances C., and MacNeal, Ward J.: The Behavior of *Escherichia Coli* and Its Specific Bacteriophage in Urine, *J. Infect. Dis.* 46:405 (May) 1930.

2. Applebaum, Martha, and MacNeal, Ward J.: The Influence of Blood and of Exudate on the Action of Bacteriophage Against the Colon Bacillus, *J. Infect. Dis.* 50:269 (March) 1932.



bacteria-free region beyond. This surgical principle should be honored by the observance rather than by the breach, as sometimes obtains in the urologic specialty.

These suggestions are not intended as reflections on the technical procedures of modern urologic instrumentation when properly employed, with adequate knowledge of the bacteriology of the urinary tract, but they are intended as a protest against ill-considered instrumental meddling with the urinary tract during the attempted application of bacteriophage therapy to this region.

Although the available evidence from autopsies and from animal experimentation is rather meager, we are nevertheless convinced that successful bacteriophage therapy of urinary infections proceeds from above downward. The bacteria are defeated and driven out of the renal substance, the renal pelvis and the ureter in turn. In the urinary bladder they are less vulnerable, possibly because of the larger volume of urine, which may have undergone undetermined changes in composition, and possibly because of folds and crypts in the mucous membrane, particularly near the vesicle neck, where the bacteria may be relatively protected. Whatever the explanation, clinical experience indicates the wisdom of stopping bacteriophage treatment when the patient has become free from symptoms and the bacterial count in the urine remains persistently below 20,000 per cubic centimeter for several days without complete sterility being obtained. One may sometimes attain final success in such instances by introducing silver nitrate in a 1 : 10,000 solution in distilled water into the urinary bladder on two successive days and following this by oral administration of methenamine and acid phosphate for two or three weeks.

Septicemia due to the colon bacillus is not common. We have had opportunity to treat only four patients with this condition in the past three years. To all of these the asparagine preparation of the bacteriophage was given intravenously, beginning with a small dose. To the three patients who survived, no dose larger than 5 cc. was given at any one time. One of these patients showed a shockingly severe reaction; another, only a slight rise in temperature, and the third, a mild chill following the intravenous therapy. The patient who died gave no reaction to the bacteriophage at any time, although the dosage was increased to 10 cc. of the undiluted preparation every two hours.

Inflammations of the large intestine which can be recognized as due to such organisms as the dysentery bacillus of Shiga have been treated by d'Herelle and others with bacteriophages with conspicuous success. Our own experience has related chiefly to stubborn colitis of long standing and uncertain etiology and to fecal fistulas persisting after surgical operations. We have not been able to recognize, in a satisfying way, the specific identity of the microbes concerned in causing the irritation

in these patients. The use of bacteriophages has, therefore, been empirical. However, one may justify a trial of bacteriophages here because their introduction into the digestive tract with the food and by colonic tube appears to be without serious untoward results and is sometimes followed by improvement which can hardly be accounted for by psychic impression alone. Ordinarily a bacteriologic study of the feces should first be made. The bacteriophages to be used are selected after test against the bacteria found. The broth-bacteriophage preparations are used, and usually several are mixed together so that the mixture will act against colon, dysentery and pyocyanus bacilli and also staphylococci. Possibly the favorable results may be due to a partial suppression of various bacteria which are acting as secondary invaders of the lesions in the intestinal mucous membrane, thus permitting the natural defenses of the body to cope more successfully with the essential cause of the disorder.

In the succeeding papers of this series we purpose to present in more detail the records of a few patients suffering from infections with colon bacilli and to indicate the mode of application of bacteriophage therapy in each case.

#### SUMMARY

The preparation of bacteriophages active against colon bacilli presents particular problems, apparently because of the complex nature of the reactions between the bacteria in this group and the multiple bacteriophage agents to be considered.

Specific bacteriologic diagnosis and isolation in culture of the offending microbes should generally precede the therapeutic use of bacteriophages. A specific bacteriophage filtrate prepared with the infecting organism should be substituted at the earliest possible moment for any stock preparation which may have been employed as an emergency measure.

The essential conditions for most effective bacteriophage action at the site of the infectious lesion should be intelligently created and maintained.

Particular technical methods of clinical application for individual patients will be indicated in succeeding papers.

# PERFORATION OF JEJUNAL ULCER INTO THE FREE ABDOMINAL CAVITY

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Jejunal (including gastrojejunal) ulcers of peptic origin are conceded to be relatively serious as compared with similar lesions in the stomach and duodenum. The seriousness of a jejunal ulcer can be attributed chiefly to the proclivity of the defect to extend rapidly beyond the wall of the intestine. This tendency is due to the thinness of the jejunum and to the inherent susceptibility to peptic corrosion of this portion of the digestive tract. The complications which develop as a result of the extension of an ulcer beyond the serous coat of the jejunum are of two principal types, penetrative and perforative. Penetration occurs when an adjacent structure becomes attached to the base of the ulcer before actual rupture occurs. Often there develops a granulomatous mass of considerable size simulating a neoplasm. Perforation generally occurs into the free peritoneal cavity or into a neighboring hollow viscus. Occasionally, however, the entire thickness of the ventral abdominal wall is perforated, and a communication between the jejunum and the exterior is established. When the rupture occurs into a hollow viscus it is the colon that is almost invariably involved. The subject of jejunocolic fistula resulting from a perforated ulcer has been extensively studied and accorded great attention in recent medical literature (Brams and Meyer,<sup>1</sup> Verbrugge,<sup>2</sup> Flörcken and Steden,<sup>3</sup> Urrutia,<sup>4</sup>

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1. Brams, W. A., and Meyer, K. A.: *Diagnosis and Treatment of Gastro-Jejunocolic Fistula*, Surg., Gynec. & Obst. **38**:646, 1924.

2. Verbrugge, J.: *Gastrojejunocolic Fistulas*, Arch. Surg. **11**:790 (Nov.) 1925.

3. Flörcken, H., and Steden, E.: *Beiträge zur Entstehung und Therapie des Ulcus pepticum jejuni (U. p. j.) nach Magenoperationen nach einigen Erfahrungen und einer Umfrage bei 22 Chirurgen*, Arch. f. klin. Chir. **143**:173, 1926.

4. Urrutia, L.: *Das Ulcus pepticum jejuni nach Magenoperationen in Spanien*, Arch. f. Verdauungskr. **40**:339, 1927.

Lahey and Jordan<sup>5</sup> and Sokolov<sup>6</sup>). On the other hand, rupture of a jejunal ulcer into the free abdominal cavity has not been the subject of a comprehensive report for many years. We deemed it desirable therefore, to investigate anew the free perforation of a jejunal ulcer, and to attempt to bring the literature up to date. As a result of this study we are able to confirm many of the statements made by previous writers and to add certain observations which we believe merit presentation. No attempt will be made to cover phases of the subject adequately treated in previous publications.

#### INCIDENCE

It is universally conceded that the free perforation of a jejunal ulcer is not of common occurrence. However, whether the condition is rare or merely uncommon appears to be an open question. The German literature particularly leads one to assume that the free perforation of a jejunal ulcer is almost a unique happening. Spath,<sup>7</sup> whose report appeared in 1927, stated that he could find accounts of only eleven perforated jejunal ulcers, three of which occurred in one patient. Spath's case of ruptured jejunal ulcer brought the number to twelve. In the statistical study by Fromme,<sup>8</sup> published two years later (1929), three cases were added, one by Porzelt<sup>9</sup> and two by himself. In the same year Just<sup>10</sup> recorded the results of his own review of the literature gathering seventeen cases of free perforation of a jejunal ulcer and adding one of his own. The latest report of a ruptured jejunal ulcer published in German periodicals is that of Steden<sup>11</sup> who, in 1931, described four cases in only three of which there was actual perforation. This brings the total, according to German writers, to twenty. This astonishingly small number is explained by the failure of the German writers to include cases reported in other languages. The figures of British authors, which embrace the cases of all countries, are much

5. Lahey, F. H., and Jordan, S. M.: Gastrojejunal Ulcers and Gastrojejuno-colic Fistulae, *Ann. Surg.* **87**:231, 1928.

6. Sokolov, S. E.: Beiträge zur Frage des Ulcus pepticum jejuni postoperativum auf Grund eines Materials von 134 Fällen russischer Chirurgen, *Arch. f. klin. Chir.* **149**:230, 1928.

7. Spath, F.: Ueber das in die freie Bauchhöhle perforierte Ulcus pepticum jejuni, *Deutsche Ztschr. f. Chir.* **205**:113, 1927.

8. Fromme, A.: Ueber primäre Resektion des in die freie Bauchhöhle geplatzten Ulcus pepticum jejuni, *Beitr. z. klin. Chir.* **147**:111, 1929.

9. Porzelt, W.: Das perforierte Ulcus pepticum jejuni im Gefolge des Zwölffingerdarmgeschwürsdurchbruchs, *Zentralbl. f. Chir.* **55**:1740, 1928.

10. Just, E.: Zur Frage des frei in die Bauchhöhle perforierten Ulcus pepticum jejuni, *Wien. klin. Wchnschr.* **42**:500, 1929.

11. Steden, E.: Ueber Ulcus pepticum jejuni mit Perforation in die freie Bauchhöhle, *Deutsche Ztschr. f. Chir.* **230**:404, 1931.

more representative of the true incidence of jejunal perforation. In 1909 a comprehensive article by Paterson,<sup>12</sup> of London, on jejunal ulcers appeared in the *Annals of Surgery*, which included summaries of nineteen cases of perforation into the free abdominal cavity. In 1918 Wright,<sup>13</sup> of Manchester, collected thirty-two cases and Massie,<sup>14</sup> of London, in 1924, increased the number to thirty-seven. In each of two patients jejunal perforation recurred, bringing the total number of perforations to thirty-nine. We have been able to add to Massie's number fifty-eight perforations occurring in forty-nine patients (text at the end of the article). The bulk of these additional reports appeared after Massie's article was written, although a few were published between 1920 and 1924. This total of ninety-seven established instances of the free perforation of a jejunal ulcer affecting eighty-six persons to which four from our own records are added, indicates that the involvement, although relatively uncommon, cannot be considered actually rare. Subsequently we shall endeavor to show that in addition to the established cases there is a relatively large group of unrecognized free jejunal perforations which, when taken into account, materially raises the incidence.

#### INCREASED DISPOSITION OF RUPTURE AFTER JEJUNAL PERFORATION

Persons in whom rupture of a jejunal ulcer into the free abdominal cavity occurs appear to be particularly predisposed to perforation in general. One indication of this tendency is the striking frequency with which previous gastroduodenal rupture occurred in the case of jejunal perforations which we found reported. Of the forty-nine patients added to those listed by Massie<sup>14</sup> the nature of the original lesion was obtained in twenty-three. In fifteen (66 per cent) of these twenty-three the initial operation was performed for a ruptured gastroduodenal ulcer. In one of the remaining eight a perforated ulcer of the stomach was the cause of the patient's fourth gastric operation, the fifth and final one being a resection for jejunal rupture. It is more than likely that statistics based on a larger number of jejunal perforations would fail to give as high an incidence of previous gastroduodenal rupture. Nevertheless, the frequency of antecedent perforation in the stomach and duodenum in the small group studied cannot be disregarded. It signifies that in at least a fair percentage of gastroduodenal ruptures treated by gastro-enterostomy subsequent jejunal perforation is to be anticipated. On account of the frequent development of jejunal perforation

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12. Paterson, H. J.: Jejunal and Gastrojejunal Ulcer Following Gastrojejunostomy, *Ann. Surg.* 50:367, 1909.

13. Wright, G.: Secondary Jejunal and Gastro-Jejunal Ulceration, *Brit. J. Surg.* 6:390, 1919.

14. Massie, G.: Perforated Jejunal Ulcer, *Guy's Hosp. Rep.* 74:70, 1924.

several authors (Spath,<sup>7</sup> Frömme<sup>8</sup> and Brandtner and Tönnis<sup>15</sup>) recommend, when possible, the avoidance of simple gastro-enterostomy in the treatment of acute gastroduodenal perforation.

Another indication of a heightened predisposition to perforation in patients with jejunal rupture is the tendency toward recurrent perforation. Repeated jejunal ruptures occurred in six of thirty of the cases collected by us. In the remaining nineteen insufficient data were available for analysis. In Robinson's<sup>16</sup> patient a jejunal perforation occurred twice at intervals of about six months. Brandtner and Tönnis<sup>15</sup> performed a gastro-enterostomy for a perforated duodenal ulcer in a patient who subsequently had two jejunal perforations four months apart. Nixon and Lowry<sup>17</sup> operated on a patient on July 3, 1921, for an ulcer on the greater curvature, seen in a roentgenogram. A posterior gastro-enterostomy was performed. In October, 1922, the first perforation, located in the stomach just above the stoma, occurred. In March 1926, a jejunal perforation took place and in August 1927, a rupture similar to the first. A fifth operation, in December 1927, disclosed multiple gastrojejunal ulcers "two about to perforate in the colon." The maximum number of true jejunal perforations occurred in the case of Riess.<sup>18</sup> In conjunction with resection of a penetrating ulcer he performed an anterior gastro-entero-anastomosis. Three consecutive perforations of the jejunum took place on Sept. 27, 1922, March 27, 1923 and March 28, 1925, respectively. Irrespective of the location, the largest number of perforations of a peptic ulcer occurred in the cases reported separately by Davenport<sup>19</sup> and Henry.<sup>20</sup> Davenport's patient was first operated on for a perforated duodenal ulcer, at which time a posterior gastrojejunostomy was performed. Subsequently a jejunal perforation occurred twice, and the anastomosis was undone. Two additional gastroduodenal ruptures followed, bringing the total to five. Henry's patient had the same number of perforations. The first was gastric, the two subsequent were jejunal, the fourth was not specified and the fifth was located at the stoma.

15. Brandtner, C. E., and Tönnis, W.: Beitrag zur Häufigkeit und Behandlung des Ulcus pepticum jejuni nach Gastroenterostomie wegen perforiertem Magen- und Duodenalulcus, *Deutsche Ztschr. f. Chir.* **236**:93, 1932.

16. Robinson, V. P.: A Case of Partial Gastrectomy for Pyloric Ulcer, Followed by Two Jejunal Ulcers Perforating at Intervals of Six Months: Recovery, *Lancet* **1**:703, 1928.

17. Nixon, P. I., and Lowry, S. T.: Multiple Consecutive Perforated Gastrojejunal Ulcers, with Report of a Case, *M. J. & Rec.* **128**:584, 1928.

18. Riess, P.: Zur Perforationsneigung des Ulcus Pepticum, *Zentralbl. f. Chir.* **52**:2818, 1925.

19. Davenport, G. L.: Five Operations in Twelve Years for Perforation, *J. A. M. A.* **97**:99 (July 11) 1931.

20. Henry, C. K. P.: Recurrent Gastric Perforations, *Surg., Gynec. & Obst.* **32**:542, 1921.

An additional manifestation of an increased susceptibility to perforation in the group of forty-nine patients with fifty-eight ruptures is found in the occurrence of six free perforations of the jejunum following gastric resection. Half the resections were wide; the other half were limited to a pylorectomy. In the case of Brandtner and Tönnis<sup>15</sup> an anterior gastro-enterostomy was performed during an operation for a perforated duodenal ulcer. A jejunal perforation followed, on which account the stomach was widely resected. Following recovery from the resection there occurred a jejunal perforation which was treated successfully by simple suture. Brütt's<sup>21</sup> patient also had a gastro-enterostomy performed following the perforation of a gastroduodenal ulcer. A year later an extensive resection of the Billroth II type was performed on account of symptoms caused by an unruptured jejunal ulcer. A year after the resection an acute perforation of a large, calloused jejunal ulcer developed for which operation was undertaken with fatal outcome. Postmortem examination disclosed two additional jejunal ulcers. Flörcken and Steden<sup>3</sup> described a case in which a gastro-jejunal ulcer developed following a pyloric resection. An extensive resection was therefore performed, following which a second jejunal ulcer developed and subsequently perforated. In January 1927, Robinson<sup>16</sup> performed a Billroth II operation on the order of a pylorectomy for the cure of duodenal ulcer. The patient was free from symptoms until August 4, when an ulcer of the jejunum perforated. The operation consisted of suturing the ulcer and covering it with omentum. On Jan. 28, 1928, a second perforation of the jejunum distal to the anastomosis occurred. Operation was again followed by recovery. The sixth jejunal perforation in this group occurred in Steden's<sup>11</sup> patient who was operated on for the first time in 1922 when a perforated pyloric ulcer was closed. The patient was subsequently operated on several times, and finally in December 1922, resection and posterior gastro-enterostomy were performed. Four years later a gastro-jejunocolic fistula developed and subsequently a jejunal ulcer perforated into the free abdominal cavity.

#### ACUTE PERFORATION OF JEJUNAL ULCER WITH SPONTANEOUS CLOSURE

Benign ruptures occurring in connection with the stomach and duodenum have been recognized for many years. These were generally referred to as "subacute" perforations (Lund<sup>22</sup> and Moynihan<sup>23</sup>). It

21. Brütt, H.: Bericht über die 34 Tagung der Vereinigung Nordwestdeutscher Chirurgen, Zentralbl. f. Chir. **54**:2268, 1927.

22. Lund, F. B.: Subacute Perforation of the Stomach with Report of Three Cases, Boston M. & S. J. **152**:516, 1905.

23. Moynihan, B. G. A.: Subacute Perforation of the Stomach and Duodenum, Ann. Surg. **45**:223, 1907.

was generally assumed that on account of the leisurely manner in which the destruction of the gastroduodenal wall occurred neighboring adhesions had an opportunity to form prior to actual rupture. The presence of these adhesions presumably led to the formation of a sac which, when perforation took place, prevented the escape of gastroduodenal content into the general peritoneal cavity. It was thought that the leakage and exudate were restricted to the preformed sac and either were absorbed or underwent suppuration leading to the development of a perigastric abscess. In 1912 Schnitzler<sup>24</sup> offered convincing evidence that at least in certain cases of perforation with a benign course rupture into the free peritoneal cavity actually occurred, but that shortly following perforation the opening was covered by a neighboring structure, usually the liver. According to Schnitzler, therefore, the adhesions which form in connection with so-called subacute ruptures result from and follow rather than precede perforation.

Singer and Vaughan<sup>25</sup> confirmed Schnitzler's conception, employing among other methods roentgenography. They found that in cases of so-called subacute perforation of the stomach and duodenum the escape of air occurs not into a perigastric pocket but rather into the free peritoneal cavity. The bubble of gas seen fluoroscopically can be made to shift to all portions of the abdomen with a change in the position of the patient. It was pointed out that in these cases of benign perforation a minute-by-minute history reveals the occurrence of sudden, violent pain identical with that of the classic rupture. Evidence was offered to show that the initial signs of subacute perforation are characteristic of diffuse peritonitis, and that the chief differences between the classic and the benign ruptures are observed subsequent to the initial manifestations, i. e., in the postperforative stage. Whereas in the classic rupture the annihilating pain of onset is followed by symptoms and signs of progressive peritonitis which does not remit until death, in the so-called subacute type the diffuse peritonitis of onset rapidly recedes, and spontaneous recovery ensues. If a patient with a benign rupture is seen for the first time several hours after the onset the manifestations are generally those of mild, retrogressing, local peritonitis. In order to emphasize the incomplete character of the clinical picture in the benign cases as compared with that of a classic perforation Singer and Vaughan suggested the term "forme fruste." The mild postperforative course in these cases is explained on the basis of early spontaneous closure of the gastroduodenal aperture.

24. Schnitzler, J.: Ueber gedeckte Magenperforationen und über die Entstehung der penetrierenden Magengeschwüre, *Med. Klin.* 1:938, 1912.

25. Singer, H. A., and Vaughan, R. T.: The "Formes Frustes" Type of Perforated Peptic Ulcer, *Surg., Gynec. & Obst.* 50:10, 1930.



Theoretically it is to be expected that the forme fruste type of rupture should occur in connection with jejunal ulcer, just as it does with gastroduodenal ulcer. That free perforation of a jejunal ulcer followed by early spontaneous closure does take place is borne out by our own experience (cases 2, 3 and 4). Regarding the incidence of forme fruste jejunal ulcers, however, little of value can be said based on the literature. It is possible that many jejunal ulcers considered to be penetrating had their origin in unrecognized perforations which sealed spontaneously. Particularly does this appear plausible when one considers the history of forme fruste perforations affecting the stomach and duodenum. Until recently it was generally assumed that benign gastroduodenal perforations were exceptional. After learning how to recognize forme fruste ruptures and instituting a search for them, one of us (H. A. S.)<sup>26</sup> observed forty instances in a period of eighteen months in one, albeit large, hospital. Subsequent experience has demonstrated that the period of observation was not unusual from the standpoint of the number of cases encountered. If the manifestations of a forme fruste jejunal perforation become generally recognized and if the possibility of its occurrence is kept in mind, the present concept of the incidence of free perforation of this type of ulcer may be altered considerably.

#### REPORT OF CASES

*CASE 1.—Perforation of jejunal ulcer into free abdominal cavity; operative closure; recovery.*

K. M., a white woman, 42 years of age, was admitted to the University Hospital on July 10, 1930, with the history that for eight years prior to 1929 she had experienced attacks of burning epigastric pain which occurred about two hours after meals and which was completely relieved by soda, milk or vomiting. In 1929 the distress was associated with persistent vomiting which did not submit to medical management. Pyloric stenosis had apparently developed, and a gastro-enterostomy was done elsewhere. The patient obtained complete relief from her symptoms, and was instructed to remain on a soft diet. About three months previous to admission she tired of the diet and ate freely of irritating foods. In spite of dietary indiscretions she had no distress until about a week before entrance when she noted bloating and nausea about a half hour after meals, followed at times by vomiting of material resembling coffee-grounds. She experienced no pain similar to that originally suffered, or any new pain left of the midline.

On the day of admission the patient was free from symptoms until 10 a. m. when she was suddenly seized by severe epigastric pain which caused her to double up. The pain rapidly spread from the epigastrium to the lower part of the abdomen, and within a few minutes of the onset it became intolerable. Vomiting occurred shortly after the initial occurrence of pain, the vomitus having the appearance of coffee-grounds. The pain continued unabated until the anesthetic was administered. Physical examination at the time of admission disclosed essentially diffuse abdominal tenderness and boardlike rigidity. The dulness of the liver was not obliterated.

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26. Singer, H. A.: Spontaneous Recovery from Perforation of Peptic Ulcer into the Free Abdominal Cavity, *Arch. Int. Med.* 45:926 (June) 1930.

ated, and no peristalsis was heard on auscultation. Siphonage of the stomach yielded 1,000 cc. of a material resembling coffee-grounds. The white blood cell count was 12,000. The temperature, pulse rate and respiratory rate were relatively normal. A diagnosis of ruptured peptic ulcer was made, and immediate operation advised.

On opening the abdomen, under ether anesthesia, a milky exudate escaped. Exploration of the stomach and duodenum revealed no evidence of a perforation. The stoma of the posterior gastro-enterostomy was then exposed, and a perforation about 2 mm. in diameter was found on the anterior wall of the jejunum 1 cm. distal to the site of anastomosis. The perforation was encircled by a moderate amount of induration. The opening was closed with three interrupted linen sutures, and an appendix epiploica, which was amputated from the transverse colon, was sutured over the site of perforation. The abdomen was closed without drainage. The patient made an uneventful recovery, and when last seen a year after the perforation was free from symptoms.

*CASE 2.—Perforation of a jejunal ulcer into the free abdominal cavity followed by formation of an abscess; operative drainage; recovery.*

B. G., a colored man, 38 years of age, first entered the Cook County Hospital on Aug. 4, 1928, on account of abdominal pain and vomiting. He had had symptoms typical of ulcer periodically since the age of 15. He was treated medically until 1915, when gastro-enterostomy and entero-enterostomy were performed. He remained well for twelve years, after which the symptoms recurred. In June, 1927, a second operation was undertaken, the gastrojejunosomy being undone and the stomach resected. The anastomosis was of the posterior Polya end-to-side type. The old entero-enterostomy was not disturbed. Following recovery the patient remained well for from six to seven months; then he began to be troubled by pain located below and to the left of the umbilicus. The pain, which was mild and localized at onset, soon increased in severity, and radiated through to the back. Food and the usual dose of sodium bicarbonate were ineffective in affording relief. At times during the attack of pain vomiting would occur, but would not be followed by cessation of pain. Morphine was frequently required for relief. Shortly after entering the hospital the patient had a profuse gastro-intestinal hemorrhage, passing several tarry stools and vomiting clotted blood. After institution of the Sippy treatment the pain disappeared, and the bleeding ceased. Roentgen examination undertaken several weeks after the hemorrhage failed to demonstrate an ulcerous niche in the remnant of stomach or in the stoma. The patient was discharged on Sept. 26, 1928, free from abdominal symptoms but still anemic.

He returned on Nov. 9, 1928, chiefly on account of symptoms referable to the persistent anemia. The pain below and to the left of the navel and in the back had returned, but was now relieved by the administration of alkalis. On November 11, two days after readmission, the patient was seized suddenly by intense periumbilical pain which rapidly spread to involve the lower part of the abdomen. He described the pain as knifelike and of far greater intensity than any pain he had previously experienced. Instead of continuously moving as he was accustomed to do in his previous attacks he remained absolutely immobile. Any attempt at change of position was associated with intense, stabbing pain. Deep breathing was also inhibited on account of resulting pain. The intern assumed that this attack of pain was similar in origin to the ones witnessed by him during the patient's first stay in the hospital. He therefore attempted gastric aspiration which seemed to aggravate rather than to relieve the pain. He then ordered morphine (¼ grain [16.2 mg.]) which afforded the patient partial relief. When

seen by an attending physician six hours after the onset of violent pain the patient was fairly comfortable. The attending physician noted a moderate amount of tenderness throughout the abdomen, with increased resistance, but no boardlike rigidity. There was little or no distention. The peristaltic sounds were decreased in number and quality. He suspected the possibility of a perforation, but hesitated to make the diagnosis because of the rapid improvement which followed the violent pain of onset and on account of the lack of classic signs. Each hour that passed found the patient greatly improved and the signs of peritonitis less definite.

We were first consulted five days after the onset of the initial violent pain because of the development of a temperature which ranged between 100 and 101 F.

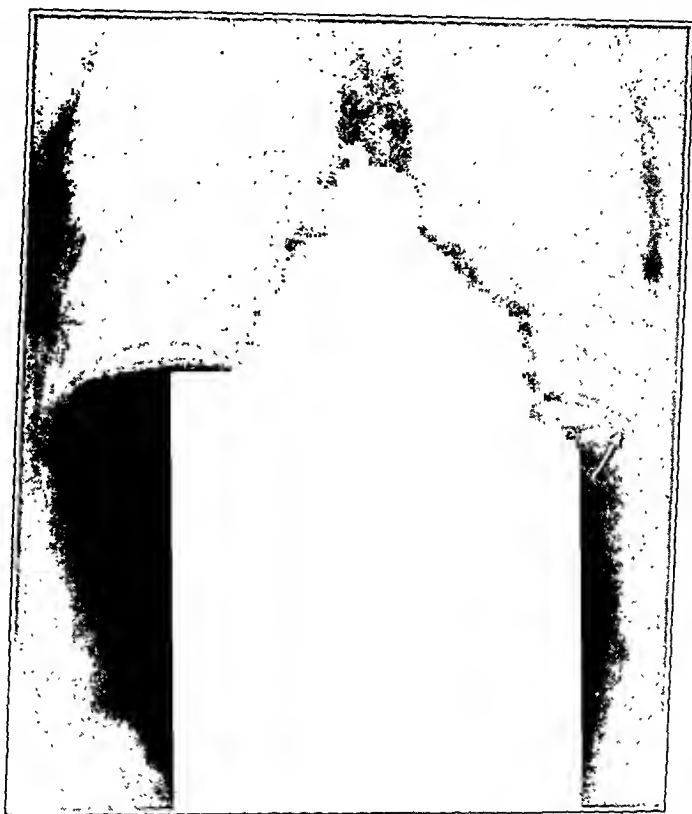


Fig. 1 (case 2).—Pneumoperitoneum due to the perforation of a jejunal ulcer. The sickle-shaped area of radiolucence beneath the diaphragm on the right side represents free air. On the left side a fluid level is seen due to liquid and gas in the stomach. Adjacent to the gastric air bubble is a small amount of free air (indicated by arrow).

On examination an ill-defined mass could be palpated in the lower part of the abdomen to the left of the midline. On the basis of the history, which was typical of acute rupture, we assumed the presence of a closed perforation with the development of an intra-abdominal abscess. Fluoroscopic examination established the diagnosis for practical purposes by demonstrating the presence of a pneumoperitoneum (fig. 1). Operation at this time was deemed inadvisable and was deferred until November 27, twelve days after the onset of the acute pain. The mass which had increased and become more definite was incised, and its purulent con-

tents drained. When the patient was discharged on Jan. 9, 1919, a small amount of drainage was still present, but the patient's general condition was good. He failed to return for further observation.

*CASE 3.—Perforation of a jejunal ulcer into free abdominal cavity in a patient with old gastrocolic fistula; spontaneous closure of recent perforation; recurrent leakage from rupture following heavy meal; operation; death.*

E. B. N., a white man, 50 years of age, was admitted to the Cook County Hospital on the evening of Dec. 23, 1929; the diagnosis made in the admission room was intestinal obstruction. The preliminary diagnosis apparently prejudiced the subsequent examiners, for the history as recorded by them indicates that they were governed by a preconceived idea. It was stated that the patient entered on account of severe abdominal pain of four hours' duration. The acute illness was preceded by symptoms of "colitis," present for a period of five months, and characterized by from twelve to fifteen evacuations a day. On the day of admission the patient ate a hearty breakfast at 8 a. m. At 10:30 a. m. he was seized with shooting pain which traveled across the middle of the abdomen, causing him to double up. The pain continued to be severe, and within thirty minutes had spread to involve the lower left quadrant, where it reached maximum intensity. The pain did not abate. No stool or flatus had been expelled since the onset.

The patient had been treated medically for peptic ulcer in 1919, and was operated on for ruptured ulcer in 1921. In 1923 a gastro-enterostomy was performed, and in 1926 the patient suffered a severe gastro-intestinal hemorrhage. Nothing was recorded regarding the character of symptoms which preceded the "colitis," nor was an attempt made to relate the diarrhea to the development of a gastrocolic fistula.

Physically the patient was described as suffering from severe intermittent pain. The presence of a cold sweat was noted. Abdominal examination disclosed two scars in the upper half, diffuse tenderness most marked on the left side and a firm tenseness of the abdominal wall which prevented palpation of the intra-abdominal contents. It was stated that peristaltic waves were not visible, but that increased peristalsis was heard on auscultation. A diagnosis of incomplete intestinal obstruction was made, although the possibility of a complication of the colitis was also considered. Enemas, gastric lavage and hypodermoclysis were instituted, following which the patient was more comfortable.

The next morning, December 24, the patient was given a barium sulphate enema which met obstruction at the sigmoid flexure, caused by what appeared to be an extrinsic mass. However, the pain had completely disappeared, and the patient was quite comfortable. On account of the decided clinical improvement operation was not deemed advisable at that time. On the following day, December 25, the patient was served Christmas dinner at noon. In the afternoon he complained of severe abdominal pain similar to that experienced on the day of onset. The pain moderated after several hours, but nevertheless was felt keenly after that time. During the next two days distention appeared, and accompanied the pain.

It was not until December 28, six days after admission, that we were consulted regarding the patient. A careful perusal of the history was sufficient to suggest the probable diagnosis. The "colitis" which was present for five months and which followed the gastro-enterostomy was considered to be the result of a gastrojejunal fistula. The sudden, intense pain which began four hours prior to admission was assumed to be due to a perforated jejunal ulcer. The subsidence of peritonitic manifestations was ascribed to spontaneous closure of the perforation. The recurrence of acute symptoms was attributed to reopening consequent to the

ingestion of the Christmas dinner. Since the patient was not improving and the possibility of a patent perforation could not be excluded, operation was recommended and undertaken immediately.

At operation the peritoneal surfaces were found to be covered with a fibrinous exudate. After wiping away the fibrin from the region of the stoma, at which point it was thickest, a perforation the size of a pinhead was exposed 4 cm. distal to the anastomosis on the anterior wall of the jejunum. The perforation was readily sutured. The colon was intimately attached to the stomach with which it communicated in the region of the greater curvature. The posterior gastro-enterostomy was undone in order to repair effectively the gastrocolic fistula. Since an

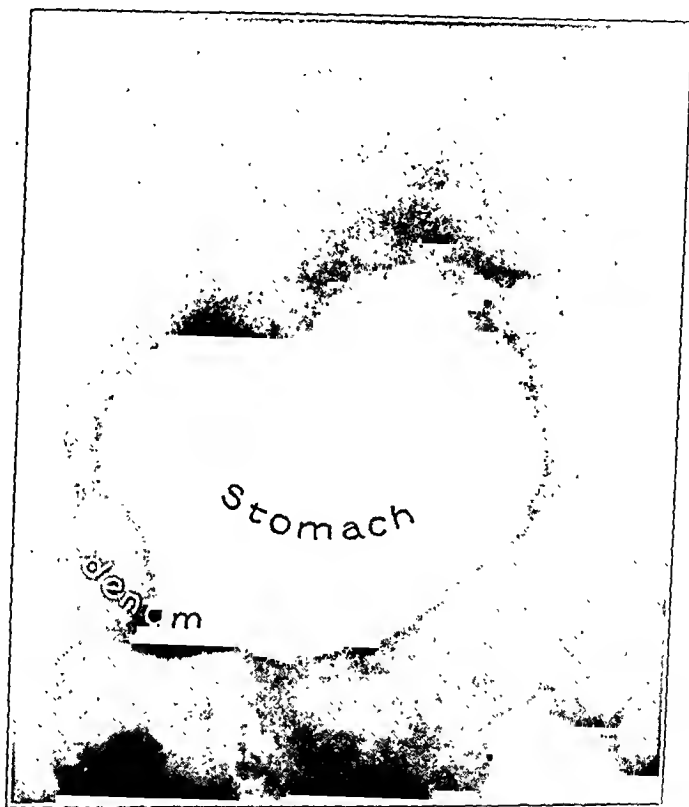


Fig. 2 (case 4).—Roentgenogram taken five hours after the administration of a barium meal. The retention in the stomach and duodenum was due to the obstruction of the proximal jejunum by the compression of an abscess following perforation of a jejunal ulcer.

obstruction existed at the duodenum it was necessary to perform another gastro-enterostomy. The day following operation signs of spreading peritonitis developed, and the patient died on December 30, two days following operation and one week after the onset of the perforation.

*CASE 4.—Perforation of jejunal ulcer into free abdominal cavity; development of high intestinal obstruction due to compression by complicating abscess; incision and drainage of abscess; recession of obstruction and recovery.*

L. H., a white man, 49 years of age, was referred to one of us (K. A. M.) on Sept. 4, 1931, for surgical relief from a duodenal obstruction. The history sub-

mitted by the referring physician stated that the patient began to suffer in 1921. The symptoms of an ulcer continued intermittently until 1924, when a posterior gastro-enterostomy and resection of the ulcer were performed. Relief was obtained for a continuous period of four years, after which an attack of epigastric pain and vomiting occurred which lasted only a few days. The patient remained well until two weeks before, when he experienced another recurrence. In spite of strict medical management the symptoms failed to submit to control, and on this account roentgen examination was proposed. A barium sulphate meal administered two days before our first examination disclosed a dilated stomach with hyperperistalsis



Fig. 3 (case 4).—The stomach and upper intestinal tract shown in figure 2 after the patient had recovered from the incision and drainage of the parajejunal abscess. The exposure was made three hours after the radiopaque meal was ingested, and demonstrates an absence of the previous duodenal obstruction.

and a greatly dilated duodenum which was apparently obstructed (fig. 2). The cause of the obstruction was assumed to be a gastrojejunal ulcer which produced narrowing of the stoma.

Our associate, Dr. Rosi, in eliciting a careful history obtained a classic account of an acute perforation which took place at the time of onset of the alleged recurrence. The intolerable initial pain, which was diffuse, gradually abated, and was replaced by a dull ache located in the left upper quadrant of the abdomen. Nausea and vomiting developed later, and became more and more persistent. Physical examination two weeks following the acute perforation led to the discovery of a

tender mass, the size of a lemon, just above the level of the umbilicus to the left of the midline. The temperature was 101.6 F., and the white cell count was 22,400. The diagnosis of perforated jejunal ulcer with subsequent formation of an abscess was made, and the obstruction attributed to the associated collateral inflammatory edema. It was thought advisable to treat the patient conservatively in the hope that the inflammation would subside and the obstruction recede. After withholding ingesta for a week and furnishing fluids, salt and dextrose by venoclysis the mass and tenderness disappeared, and the temperature and white cell count returned to approximately normal. The patient was then given a liquid diet, and appeared to be doing well for six days, but on the following day he vomited 1,500 cc. of material. Operation was therefore decided on, and performed on September 19.

After reflecting the transverse colon upward and exposing the site of the gastro-enterostomy an abscess was encountered lying between the angle formed by the afferent and the efferent loops. The abscess compressed and narrowed the adjacent bowel, and was apparently responsible for the obstruction. The gastro-enterostomy stoma was widely patent, having a breadth of three fingers. The pus was evacuated and the cavity of the abscess drained. No attempt was made to search for the jejunal perforation. The convalescence was uneventful, and the patient was discharged feeling well. Roentgen examination undertaken following recovery from operation showed no dilatation of the stomach or duodenum, but a poorly functioning gastrojejunal stoma (fig. 3).

#### COMMENT

The account of case 1 is a classic description of a jejunal perforation into the free abdominal cavity. It is typical of the clinical picture which characterizes the cases reported in the literature. In the other three cases jejunal perforation occurred likewise into the free abdominal cavity. However, the clinical picture was different, and careful analysis was necessary to establish the fact that acute rupture had occurred. In the second case an intra-abdominal abscess was traced to an acute perforation which was not recognized as such by the attending physician who saw the patient early. The lack of recognition of the rupture was due to the spontaneous closure of the perforation and the limitation of jejunal leakage. The evidence in this case for perforation into the general abdominal cavity rather than into a preformed sac was afforded by fluoroscopy which demonstrated that the escaped air was free. The genesis of the abdominal abscess is presumably the same as in perigastric abscess following rupture of the stomach or duodenum. It has been shown by Singer and Rosi<sup>27</sup> that intraperitoneal accumulations of pus complicating gastroduodenal perforation are the result of encapsulation of exudate following and not preceding rupture.

In the third case the patient was thought to be suffering from an intestinal obstruction. However, the history indicated clearly that the

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27. Singer, H. A., and Rosi, P. A.: The Pathogenesis of Perigastric Abscess Complicating Peptic Ulcer, *Am. J. M. Sc.* **183**:600, 1932.

symptoms and signs at the outset were those of diffuse peritonitis, and that localization did not occur until some time later. Apparently spontaneous closure of the opening in the jejunum occurred shortly following rupture, and the escaped material was absorbed by the peritoneum. A second attack of severe pain two days subsequent to the first occurred following the intake of a heavy meal. Here also the manifestations were those of diffuse peritonitis due presumably to the separation of fibrinous adhesions and the reopening of the perforation. The bewildered clinicians were unable to reconcile the clinical history with the physical observations. As the operation subsequently demonstrated, sealing of the perforation was accomplished by nature following the second rupture also. However, the closure of the aperture was not effected soon enough or was not sufficiently secure to prevent the escape of enough material to produce moderately severe peritonitis. The confusing element in the case was the intermittent leakage, a phenomenon which has been observed previously in connection with gastroduodenal perforations (Singer<sup>28</sup>). Death might have been averted if the surgical procedures had been limited to the acute aspects of the case, and the old gastrocolic fistula had been dealt with at a more favorable time. When first seen, the patient in the fourth case presented roentgenologic and clinical evidence of a high intestinal obstruction. The history led to the diagnosis of a recent free perforation of a jejunal ulcer complicated by the formation of an abscess. The pathogenesis of the abscess was presumably similar to that complicating the rupture in case 2.

It is difficult to estimate the incidence of free perforation of jejunal ulcer followed by spontaneous closure. In the literature dealing with rupture of jejunal ulcer an occasional reference (Urrutia,<sup>4</sup> Brütt<sup>29</sup>) is made to the occurrence of a "covered" perforation. It appears, however, particularly in the case of Brütt, that the adhesions which were found about the base of the ulcer might have preceded rather than followed the destruction of the serosa. The lack of published reports on the free perforation of the jejunum with spontaneous closure would seem to indicate that this sequence is rare. Our own experience, unless unique, would signify otherwise. It is more than likely that some cases of jejunal ulcer characterized by severe pain and diagnosed as penetration or subacute perforation represent acute ruptures with subsequent spontaneous sealing of the hole. Careful attention should

28. Singer, H. A.: Perforated Peptic Ulcer with Intermittent Leakage, *J. A. M. A.* **102**:112 (Jan. 13) 1934.

29. Brütt, H.: Beiträge zur Klinik und zur operativen Behandlung des peptischen Jejunalgeschwürs nach Gastroenterostomie, *Beitr. z. klin. Chir.* **126**:41, 1922.



be paid to the details of onset and the subsequent developments in patients on whom gastro-enterostomy has been done and who experience severe abdominal pain. A proper analysis of such cases, plus a knowledge of the mechanism of a forme fruste rupture may lead to the realization that the free perforation of jejunal ulcer occurs relatively oftener and that many free perforations pass unrecognized.

#### SUMMARY

A statistical survey of the literature on the perforation of jejunal ulcer into the free abdominal cavity yields a total of ninety-seven instances occurring in eighty-six persons. A striking feature in patients who have a rupture of a jejunal ulcer is the increased disposition toward perforation. The enhanced perforative tendency is indicated by the frequency of previous gastroduodenal rupture and recurrent jejunal perforation even following resection.

Four cases of rupture of jejunal ulcer into the free peritoneal cavity are reported. The first example is of the classic variety, and is typical of the cases reported in the literature. The other three instances are atypical in that two were characterized by the formation of an abscess and the third by evidence of intermittent attacks of perforative peritonitis. In analyzing carefully the two cases with abscesses, the initial symptoms were found to be characteristic of diffuse peritonitis. The clinical manifestations indicated primary free perforation with spontaneous closure of the hole and localization of the exudate. In one case the presence of a movable intraperitoneal bubble of gas served to substantiate the opinion that the rupture occurred into the free abdominal cavity. In the case with intermittent symptoms the initial perforation was of the forme fruste type; that is, the rupture was accompanied by a minimum amount of leakage, owing to prompt, spontaneous sealing of the aperture. A hearty Christmas dinner was followed by a recurrence of symptoms presumably due to the separation of the fibrinous adhesions and reopening of the hole. With better appreciation of the manifestations of free, acute perforation of a jejunal ulcer followed by spontaneous closure the diagnosis of penetration or "sub-acute" perforation will not be made as often as heretofore. Furthermore, it is believed that the recognition of atypical cases will indicate that the free perforation of a jejunal ulcer is not uncommon.

#### RECENT CASES REPORTED IN THE LITERATURE

The following list does not include the thirty-four cases collected by Massie.<sup>14</sup> The number of cases recorded by each author is indicated in the figure or figures preceding each name.

1-2. Ashcroft, A. T.: Two Cases of Perforated Jejunal Ulcer, *Brit. M. J.* 1:528. 1926.

3. Brandtner and Tönnis.<sup>15</sup>
4. Brütt.<sup>21</sup>
5. Bundschuh: Zur Frage der Resektion beim freiperforierten Magen-Zwölfingerdarmgeschwür, *Arch. f. klin. Chir.* **129**:281, 1924.
6. Davenport.<sup>19</sup>
7. Ehrlich, S. P.: Repeated Perforations of Peptic Ulcers with Recovery, *J. A. M. A.* **90**:1870 (June 9) 1928.
8. Flörcken and Steden.<sup>3</sup>
- 9-11. Fromme.<sup>5</sup>
12. Henry.<sup>20</sup>
13. Jura, V.: Perforation of Jejunum Following Gastro-Enterostomy for Duodenal Ulcer, *Boll. e atti d. r. Accad. med. di Roma* **53**:131, 1927.
14. Just, E.: Zur Frage des frei in die Bauchhöhle perforierten Ulcus pepticum jejuni, *Wien. klin. Wchnschr.* **42**:500, 1929.
- 15-16. Kunz, H.: Ueber das perforierte Magen-Duodenalgeschwür und das perforierte pepticum jejuni, *Arch. f. klin. Chir.* **140**:419, 1926.
- 17-18. McKelvey, J. L.: Perforated Gastro-Jejunal Ulcer, *M. J. Australia* **2**:414, 1922.
19. Nixon and Lowry.<sup>17</sup>
20. Porzelt.<sup>9</sup>
21. Recht, H.: Aeussere Spontanfistel bei postoperativem Ulcus pepticum jejuni, *Deutsche Ztschr. f. Chir.* **224**:344, 1930.
22. Riess.<sup>18</sup>
23. Roberts, A. T.: A Case of Perforating Jejunal Ulcer Following Posterior Gastro-Enterostomy, *M. Press & Circ.* **109**:480, 1920.
24. Robinson.<sup>16</sup>
- 25-27. Schwarz, E.: Ueber die operative Behandlung des perforierten Magen- und Duodenalgeschwürs und der Perforation des peptischen Jejunalulcus nach der Gastroenterostomie, *Deutsche Ztschr. f. Chir.* **192**:239, 1925.
- 28-30. Sokolov.<sup>6</sup>
40. Spath.<sup>7</sup>
- 41-43. Steden.<sup>11</sup>
44. Steinberg, M. E.: Acute Perforation of Jejunal Ulcer, *Northwest Med.* **23**:187, 1924.
- 45-47. Urrutia.<sup>4</sup>
48. Winkelbauer, A.: Zur Frage des postoperativen Ulcus pepticum jejuni, *Arch. f. klin. Chir.* **140**:427, 1926.
49. Zeno, A.: Perforation of Jejunal Ulcer After Operation on Perforated Duodenal Ulcer, *Rev. méd. del Rosario* **1**:150, 1926.

NOTE.—Since the present article was submitted for publication a fifth case of perforated jejunal ulcer has been observed by us:

A man, aged 43, had suffered from symptoms of ulcer since 1903. Eventually evidence of pyloric obstruction appeared, on which account a gastro-enterostomy was performed in 1920. On Jan. 10, 1934, he suffered from acute perforation of an ulcer located at the stoma. At operation, performed eleven hours after the initial pain of rupture, the aperture was found to be concealed by fibrin. Suture of the perforation was followed by uneventful recovery.

# PEPSIN IN THE PREVENTION OF ABDOMINAL ADHESIONS

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There are many controversies concerning the use or abuse of methods for the prevention of adhesions, and sides are taken by men of equal renown. Favoring the advancement of the study of prevention of adhesions are men who have devoted much time to experimentation to prove or disprove certain theories. Among them are Payr, Vogel and Sidorenko, and more recently Kubota, Ochsner, Warren and Trusler. On the other hand, some have abandoned all hope of finding a substance which will take nature's place, and most prominent among them are Hertzler, D. F. Jones and W. L. McClure. The subject is concrete and lends itself to experimentation.

The purpose in view in all work of this type is not so much to prevent entirely the formation of all adhesions as to limit their formation to such an extent that they may not result in complications. It is not the adhesions, but the complications resulting from them which account for the fatalities attributed to them. Adhesions are desirable to a certain extent, for without them there would be innumerable postoperative fatalities. They constitute a natural process of protecting the peritoneal cavity from the spread of infection, and thereby limit the absorption of toxins when these are present. When no infection is evident, they represent nature's method in the healing process, but frequently they reach such proportions as to be not only undesirable, but dangerous.

In 1923 Deaver<sup>1</sup> classified adhesions as congenital and acquired; of the latter group he mentioned the inflammatory and operative types, but since injury to the peritoneum results in the same changes as an inflammatory process without infection we can classify these two as one. Of inflammatory adhesions he said that they may be constructive or destructive, which is analogous to Hertzler's<sup>2</sup> classification of physio-

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Prepared with the aid of a grant from the Isaac Kaufmann Foundation.

1. Deaver, J. B.: *Intra-Abdominal Adhesions*, Surg., Gynec. & Obst. **37**:506, 1923.

2. Hertzler, A. E.: *The Peritoneum*, St. Louis, C. V. Mosby Company, 1919, vol. 1.

logic and pathologic adhesions: physiologic if they degenerate after their function is performed, and pathologic if they become progressive and permanent. Physiologic adhesions are essential, when their need is urgent to help prevent the spread of infections. But, these adhesions take place early, sometimes within a few hours from the time trauma has been induced (MacCallum<sup>3</sup>), although the fibrin is deposited from ten to thirty minutes from the time the injury has taken place. The adhesions are expected to retrogress. Whether they do or not depends on several factors, among the most important of which are the individual tendency of the patient, too extensive trauma and the extent of the infection. There are certain adjuncts within the power of the operator which tend to limit the formation of adhesions, but these do not solve the problem. The solution lies, as Jones and McClure<sup>4</sup> put it, in the imitation of nature's method of prevention and ablation of adhesions. With this principle in view, the studies reported here deal especially with the biochemical action in the development and the retrogression of adhesions.

The manifestations of the process involved in the formation of adhesions will be modified by the anatomic surroundings and the physiologic activity of the peritoneum. It is necessary, therefore, to have a clear understanding of the anatomy, physiology and pathologic physiology of the peritoneum before one can undertake to alter the normal mechanism. The omentum is a peritoneal organ which plays a great part in physiologic activity in the process of repair. It is covered by a flat layer of endothelial cells, any injury to which calls forth great protective action on its part. The great rôle of the omentum is to wall off the site of an infection by adhering to it and thus preventing spread of the infection. It is well known that the omentum has a particular tendency to cling to roughened or infected surfaces. The parietal peritoneum lines the cavity and the visceral peritoneum covers the organs as a whole or in part, depending on their position and relation. Its function is primarily twofold: (1) to provide a smooth surface so that the organs may have free gliding movements during their normal activity, and (2) to absorb excess secretion in the cavity. Experiments have been performed to determine the route of the absorption with diphtheria toxin used as the agent. The conclusion was that the toxin was absorbed through the blood stream as well as through the lymphatic system. Though there is some controversy the route of absorption is irrelevant here. But what is of concern is that absorption takes place with remark-

3. MacCallum, W. G.: *Text Book of Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

4. Jones, D. F., and McClure, W. L., in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 7, chap. 8, p. 49.

able rapidity. This is one of the factors to bear in mind when using solutions to inhibit the formation of adhesions. Experimental animals have absorbed as much as 8 per cent of their body weight in one hour. If the amount injected does not exceed 10 per cent of the body weight, 30 per cent or one third of the solution is absorbed in thirty minutes. The rate of absorption varies with the character and density of the fluid used, and may be delayed by peristalsis, because it is by peristalsis and the excursion of the diaphragm that the fluid injected is moved about. Since the rate of absorption is rapid, we therefore see that any substance introduced must be beneficial by virtue of its initial and rapid action as well as of its other properties.

During an insult to the peritoneum, by either chemical or mechanical means, there is an immediate deposit of fibrin on the surface. This process is comparable to an inflammatory reaction; it increases the tendency for adjacent surfaces to adhere and is responsible for the formation of fibrinous and then of fibrous adhesions which may eventually prove to be permanent and dangerous. The deposition of bundles of fibrin has been observed by Hertzler as early as ten minutes following the approximation of surfaces; the process is usually completed in two hours, and after six hours the adhesions are fairly firm. The rapidity with which these fibers are laid down is emphasized by the observation that during an operation for a gastro-enterostomy the first line of sutures is completely covered by fibrin by the time the operation is completed. The entire mechanism of the peritoneum is concerned with the attempt to localize and limit the extent of serosa involved.

Lacey<sup>5</sup> says that in the early reaction to an inflammatory process there is local leukocytosis, and that through the action of proteolytic ferments resulting from the leukocytosis the exudate which forms is absorbed. Consequently there is a dissolution of the products which results in adhesions. To duplicate this process artificially it would be necessary to devise some way of imitating nature's method and to bring about the resorption of those products the presence of which sometimes results disastrously for the patient and becomes a source of embarrassment to the surgeon.

The factors which increase the dangers of formation of adhesions are: (1) exposure and handling of viscera by the use of force, dry sponges and packing; (2) infection; (3) blood in the presence of an abrasion and a collection of blood in the cavity; (4) chemical irritation by iodine, iodoform and ether; (5) the use of a cautery; (6) sutures and ligatures; (7) subperitoneal hematoma, and (8) substances introduced for the prevention of adhesions.

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5. Lacey, J. T.: *Ann. Surg.* 92:281 (Aug.) 1930.

## REVIEW OF THE LITERATURE

Some of the substances and methods used for the prevention of adhesions bring about the very thing which they were expected to prevent. Of the literature on this subject, the most logical and complete review is the outline of Ochsner and Garside,<sup>6</sup> in which they mentioned first the mechanical methods employed: the omental grafts suggested by Nicholas Senn in 1888 and peritoneal flaps. In 1894 the use of foreign substances was first introduced; among the first were fish bladder and the peritoneum of a calf, sterilized ox peritoneum or Cargile membrane, oiled silk and silver foil. Then a series of substances was used apparently for their lubricating effect: sterile olive oil, petrolatum and camphor liniment, the use of which was recommended by such authorities as Pfannenstiel, Hahne and Seuffert. Hydrous wool fat, U. S. P., a brand of thymol iodide, paraffin, acacia, gelatin mucin and albumin of egg were used. To demonstrate to what extreme science will go, reference is made to a Dr. Pribram who advocated the use of the vitreous humor of calves' eyes. Simultaneous with the use of these more or less solid substances, a series of experiments was carried on with the idea of keeping the serous surfaces apart, and in this group saline solution, citrate, dextrose and a combination of the last two were used. Among other methods mentioned are the use of oxygen in the cavity, high enemas, filling of the bladder, the administration of peptone and thiosinamine and stimulation of peristalsis. All of these methods were tried and in the final analysis were found wanting. More recently Johnson<sup>7</sup> reported his work on the use of amniotic fluid prepared in one of several ways. His results were excellent and were corroborated by Warren<sup>8</sup> and Trusler.<sup>9</sup> Lacey<sup>5</sup> repeated the experiments, but did not get the same results, although he admitted that the fluid might modify the density of the adhesions.

The final era in this type of work began with the use of digestive ferments in the prevention of abdominal adhesions. A number of investigations are recorded concerning the efficiency of these ferments.

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6. Ochsner, A., and Garside, Earl: *Surg., Gynec. & Obst.* 54:338 (Feb.) 1932.

7. Johnson, H. L.: *Amniotic Fluid Concentrate in the Prevention of Adhesions*, *New England J. Med.* 199:661, 1928; *Observations on the Prevention of Post-Operative Peritonitis and Abdominal Adhesions*, *Surg., Gynec. & Obst.* 65: 612 (Nov.) 1927.

8. Warren, Shields: *Effect of Amniotic Fluid on Serous Surfaces*, *Arch. Path.* 6:860 (Nov.) 1928.

9. Trusler, H. M.: *Peritonitis: Experimental Study of Healing in the Peritoneum and the Therapeutic Effect of Amniotic Fluid Concentrate*, *Proc. Staff Meet., Mayo Clin.* 4:356 (Dec. 11) 1929.

Stewart<sup>10</sup> described an experiment which would make one believe that the action of pepsin results in the absorption or digestion of fibrin. Theoretically, then, it may be assumed that in this manner the fibrin which is formed on the irritated peritoneum is also digested by the pepsin. In 1922 Payr<sup>11</sup> first used a product which he called pepsin-Pregl solution which consisted of pepsin as the digestant and Pregl's solution, the latter being added to sterilize the ferment. Ochsner stated that Frankenthal corroborated the experiments and found that the substance inhibits the formation of adhesions. Kubota was unable to confirm this. Convinced of the futility of the numerous other substances, Kubota tried papain as the digestant of choice and obtained satisfactory results. With his results as an incentive Ochsner<sup>12</sup> used a solution of papain in various strengths and found that in solution ranging from 1:100,000 to 1:400,000 the activity was effective. He also used trypsin, but was not satisfied. He found that its action was inhibited by antitrypsin, which is normally found in exudates and transudates. He continued then with the papain, but encountered some difficulty in the solubility of the product, and the experimentation for a time was abandoned.

#### EXPERIMENTAL WORK

Continuing on the theory that the use of digestive ferments is rational, we decided to use an extract of pepsin, first in hydrochloric acid and then in glycerin, but free from iodine. We knew the powerful antiseptic property of iodine, since it was demonstrated by placing 1 drop of the standard 7 per cent solution of iodine in 3 ounces (85.02 Gm.) of culture medium; in this strength it inhibited the growth of bacteria. We also learned that 2 per cent iodine was successfully used as an irritant to the peritoneum by Johnson.<sup>7</sup> In view of these facts, we wonder, then, if the iodine in Pregl's solution did not exert some influence in counteracting the beneficial effects of the pepsin. With this in mind, pepsin without iodine was introduced. The method followed in extracting the pepsin required the use of an acid medium to effect as complete an extraction as was desirable. This need not be hydrochloric acid. We determined the hydrogen ion concentration by titration with the following results: pepsin extracted with hydrochloric acid gave a result of  $p_H$  5.21 and pepsin extracted with glycerin,  $p_H$  6.5. This showed that we had an acid extract. We further observed that pepsin extracted with glycerin digested blood clots in vitro.

Prior to the use of pepsin, we attempted to prove or discard the results of some experiments previously attempted. In the control experiment with rats the results after trauma with no agent introduced into the cavity were 100 per cent dense adhesions. We employed a 1:1,000 solution of urease and also obtained 100 per cent adhesions. Thiosinamine had been used by Offergell, Mitchell, Bush and Bibergeil with moderately good results. Our work with this drug showed that 58 per cent of the animals had from fine adhesions to none and that 16 per

10. Stewart, G. N.: *Text Book of Physiology*, ed. 8, New York, William Wood & Company, 1918.

11. Payr, E.: *Ueber postoperative und spontane Adhaesionen in der Bauchhoehle*, *Zentralbl. f. Chir.* **41**:99, 1914.

12. Ochsner, Alton: Personal communication to the authors.

cent of this number had no adhesions. Forty-two per cent had dense or moderate adhesions. This shows some measure of success. A proprietary preparation of bovine amniotic fluid was used and our results show 37 per cent dense or moderate and 63 per cent fine adhesions, somewhat more in keeping with the results of others, (Lacey<sup>5</sup>), but not as optimistic as the results of Trusler,<sup>9</sup> Johnson<sup>7</sup> and Warren.<sup>8</sup> Though our results showed 63 per cent of fine adhesions no incision was entirely free. These experiments were conducted on rats, and covered a total of 74 operations on 32 animals.

In our work with pepsin we used 44 animals, on which 104 laparotomies were performed. Most of the animals survived the several operations, but in those that died, we did not find a single case of intestinal obstruction at autopsy. Peritonitis and hemorrhage were the causes of death in all cases.

To produce adhesions which may be considered permanent, there must be sufficient trauma to produce an exudate capable of forming fibrin to a marked degree. Such a process may be set up by chemical irritation, by infection or by mechanical violence. In our series we determined by means of controls that the simple handling of the viscera resulted in the formation of adhesions in 6 of 8 cases, or 75 per cent, and when we traumatized with gauze we had adhesions in 8 of 10 cases, or 80 per cent. We therefore used the latter method.

The abdomen, from which the hair had been clipped close and to which iodine had been applied, was entered through a midline incision, and the small intestine was vigorously rubbed with a gauze-covered finger for a distance of from 6 to 8 inches (15 to 20 cm.) in several places. The peritoneum on each side of the

#### *Adhesions Resulting from Operation on the Controls*

	Number of Animals	Percentage of Adhesions			
		Class 1		Class 2	
		Number	Per Cent	Number	Per Cent
With trauma.....	10	2	20	8	80
Without trauma.....	8	2	25	6	75

incision was forcibly scraped with the sharp end of a scalpel. The contents of the abdomen were replaced and the abdomen was closed in layers, catgut being used for the peritoneum and dermal for the skin. Before the peritoneum was closed we instilled the fluid.<sup>13</sup> When the abdomen was reopened and required extensive separation of adhesions, we did not employ further trauma, except incident to separation.

For the purpose of classification we further subdivided the pathogenic adhesions into four types: (1) filmy (very fine cobweb strands, viscerovisceral or visceroparietal, easily separated); (2) fine (small strands of fibroconnective tissue uniting the viscera to the visceral or to the parietal peritoneum, easily separated); (3) moderate (the viscera adherent to the visceral or to the parietal peritoneum by contact or by bands requiring moderate force to separate them); (4) dense (fibrous adhesions between the viscera or between the viscera and the parietal peritoneum

13. The extracts of pepsin used in our experiments were prepared under the supervision of Dr. Sharp and Mr. Taylor of the Parke-Davis Laboratory. The active principle of pepsin was extracted from hog stomach with a 0.4 solution of hydrochloric acid and with glycerin and water. The strengths we used ranged from 0.5 to 2 per cent.



requiring considerable force or section to separate, usually resulting in extensive trauma to the tissues involved and sometimes accompanied by bleeding).

We divided the cases into two classes: class 1, those in which we obtained filmy, fine or no adhesions, and class 2, those in which moderate or dense adhesions resulted. We used the hydrochloric acid extract in one series and the glycerin and water extract in another. The results follow:

Group 1 (hydrochloric acid).—Nineteen operations were performed; 45.5 per cent of the cases were in class 1, and of these 25 per cent showed no adhesions.

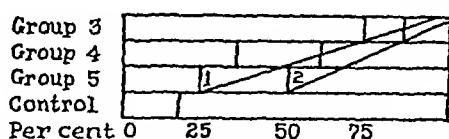


Fig. 1.—A composite graph showing prevention and alleviation curve in groups 3, 4 and 5 and in controls.



Fig. 2 (rabbit 28).—Third operation without injection eighteen days after lysis. The dense adhesion between the omentum, the small bowel and the peritoneum is notable.

Group 2 (glycerin and water).—Twenty-two operations were performed; 63.2 per cent of the cases were in class 1, and of these 39.1 per cent showed no adhesions. (Since the glycerin and water extract gave better results, we continued our experiments with this solution.)

Group 3 (glycerin and water, 0.5 per cent; traumatized by scarification).—Twenty-two operations were performed; 86.4 per cent of the cases were in class 1, and of these 75.8 per cent showed no adhesions.

Group 4 (glycerin and water, 0.5 per cent; lysis without further irritation).—Twenty-one operations were performed; 62 per cent of the cases were in class 1, and of these 33 per cent showed no adhesions.



Fig. 3 (rabbit 15).—Third operation fourteen days following lysis; 50 cc. of 0.5 per cent pepsin in a solution of glycerin and water was injected. The adhesion of the appendix to the small bowel and to the peritoneum is apparent.



Fig. 4 (rabbit 19).—Fourth operation twenty-one days following lysis of a matted small bowel and an adhesion between the omentum and the appendix; 75 cc. of pepsin in a solution of glycerin and water was injected. There is one dense adhesion between two loops of the small bowel.



Fig. 5 (rabbit 35).—Twenty-two days after irritation and an injection of 50 cc. of 0.5 per cent of pepsin in a solution of glycerin and water. The one fine adhesion between the small bowel and the appendix can be seen.



Fig. 6 (rabbit 38).—Operation thirteen days after a primary irritation (the small bowel was torn in the process and was repaired). Fifty cubic centimeters of pepsin in a solution of glycerin and water was injected. The repaired section of the bowel is adherent to the lower angle of the incision, and there are numerous cobweb adhesions.



Fig. 7 (rabbit 37).—Operation twenty-four days after a primary operation, when the tissues were irritated. Fifty cubic centimeters of 0.5 per cent of pepsin in a solution of glycerin and water was injected. There are scars on the irritated section of the small bowel free from adhesions; edema of the mesentery is evident.



Fig. 8 (rabbit 27).—Operation thirty days after a primary irritation. Fifty cubic centimeters of 0.5 per cent of pepsin in a solution of glycerin and water was injected. The absence of adhesions is noticeable.

foreign substance introduced into the cavity. The factors active during such times are very definite. The close approximation of inflamed surfaces results in delayed absorption of fibrin, which is not subject to attack as on exposed surfaces. We do not see how a substance injected would interfere with the formation of physiologic adhesions when infection is present and when adhesions are necessary. The formation of adhesions is dependent on deposits of fibrin and the quantity of fibrin deposited at any given point is in turn dependent on several factors, among which are: (1) the extent of the trauma, and (2) the extent of the infection. Though cases are found in which considerable trauma was used or in which infection was present, but in which no adhesions were found later, these cases were the exception and not the rule.

We think it can be assumed that the rôle of fibrin, when it is required, is not destroyed by foreign substances and that when adhesions are desirable fibrin is present in sufficient amount to ward off the invasion of a foreign substance.

#### SUMMARY

Attempts have been made for forty-five years to introduce methods for the prevention of adhesions, but all have been discarded. The benefit of digestive ferments has not been disproved. Thiosinamine has not been effective in our experiments. A *proprietary preparation* of bovine amniotic fluid gave favorable results. Pepsin, as a digestant, has been suggested experimentally to be an adjunct to the general principles of good surgery in the prevention of adhesions. Pepsin extracted with hydrochloric acid was not promising as a preventive, but in a glycerin and water extract it was effective in its prevention or reduction of the reformation of adhesions in 62 per cent of the cases. Pepsin was most effective as a prophylactic in primary operations in 86.4 per cent of the cases.

PROGRESSIVE OBSTRUCTIVE JAUNDICE  
CHANGES IN CERTAIN ELEMENTS OF THE BLOOD AND THEIR  
RELATION TO COAGULATION

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In 1618, according to Thudichum,<sup>1</sup> Johannes Fabricius removed gallstones from the gallbladder of a living subject. Fabricius Hildanus refers to this operation in his "Surgical Observations," but it is not clear whether the operation was premortem, as the only evidence of the subject's being alive is the somewhat dubious expression "*delineatio horum lapidum ad vivum facta.*"

No such shadow hangs over Petit's<sup>2</sup> first project. During the decade beginning with 1733 he discussed boldly and with great acumen tumors of the gallbladder and the sequences of biliary obstruction. From these papers and the discussion which arose over them he emerged as the founder of gallbladder surgery, his description of symptoms and outlines of operative procedures remaining classic.

Neither Petit nor Thudichum, who wrote with equal insight a century and half later, failed to evaluate the difficulties of gallbladder surgery excepting one. Neither mentioned the hemorrhagic tendency in obstructive jaundice which today stands as one of the most difficult and perplexing problems confronting the modern physician. Nor did Bobbs<sup>3</sup> of Indianapolis, who fathered the modern cholecystotomy, or Langenbuch<sup>4</sup> in 1882, who is credited with the first cholecystectomy, refer to the dangers of postoperative hemorrhage although their statistics would have been better and the results of Thiriar and Courvoisier after them would have been more successful had they known of the danger of hemorrhage and of a way to control it.

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This work has been conducted under grants from the Christine Breon Fund for Medical Research and from the Research Budget of the Department of Pathology of the University of California Medical School.

1. Thudichum, J. L. W., quoted by Smith.<sup>5</sup>

2. Petit, J. L.: *Mém. Acad. roy. de chir.* 1:163, 1743.

3. Bobbs, J. S.: *Tr. Indiana State M. Soc.*, 1868, p. 68.

4. Langenbuch, quoted by Smith.<sup>5</sup>

The modern surgeon stands superior to these venerable pioneers in technical knowledge and skill and knows of the danger from hemorrhage since Greig Smith<sup>5</sup> remarked on it forty years ago, but in spite of an enormous investigative effort and the propagation of innumerable theories he knows no more of the reason for, or of the method to control, this bleeding than did Martin Sims<sup>6</sup> or Petit or Johannes Fabricius before him.

All the theories as to the cause and the treatments based on them to date have concerned themselves with deficiencies in one or another of the formed clotting elements of the blood in spite of the fact that various observers have at different times found each of these elements to be normal, even in extreme examples. It is true that Howell<sup>7</sup> proposed a deficiency in heparin as the possible cause of bleeding, but aside from this one instance investigators have believed and attempted to prove that a variation in one or more of the formed clotting elements is responsible for death due to hemorrhage of these unfortunate persons.

The first of these theories apparently developed from the work of Rohig,<sup>8</sup> who believed that the circulating bile salts (taurocholate and glycocholate) were responsible for the bradycardia and lowered blood pressure. King and Stewart<sup>9</sup> repeated his work in 1909 and in addition to duplicating his result discovered that bile pigments in combination with the simple salts of calcium were less toxic than when given alone. They concluded that the reserve blood calcium was used up in combining with excess bile pigments and therefore was not available for coagulation.

Many years later W. Walters<sup>10</sup> published the results of autopsies on thirty jaundiced patients who died after abdominal operation. Half of these had large intraperitoneal hemorrhages which he accounted for by assuming a deficiency in calcium. He cited the work of Lee and Vincent,<sup>11</sup> who found that the addition of calcium chloride to jaundiced blood in the test tube shortens the coagulation time. Reasoning from this he advocated the use of calcium chloride intravenously in jaundiced patients. This medication met with some success and is still being used.

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5. Smith, Greig: *Abdominal Surgery*, Philadelphia, P. Blakiston's Son & Co., 1891, p. 610.

6. Sims, Martin: *Brit. M. J.* **1**:811, 1878.

7. Howell, W. H.: *Am. J. Physiol.* **77**:680 (Aug.) 1926.

8. Rohig, J.: *Arch. d. Heilk.* **4**:385, 1863.

9. King, J. H., and Stewart, H. A.: *J. Exper. Med.* **11**:673, 1909. King, J. H.; Bigelow, J. E., and Pearce, L.: *J. Exper. Med.* **14**:159, 1911.

10. Walters, Waltman: *Surg., Gynec. & Obst.* **33**:651 (Dec.) 1921.

11. Lee, R. I., and Vincent, B.: *The Relation of Calcium to the Delayed Coagulation of the Blood in Obstructive Jaundice*, *Arch. Int. Med.* **16**:59 (July) 1915.

The benefit, however, is not due to replacement of deficient blood calcium but to an entirely different mechanism which will be discussed later.

Immediately following publication of the theory on calcium deficiency many workers made determinations of blood calcium on jaundiced patients and on experimental animals. Halverson, Mohler and Bergeim<sup>12</sup> reported a slight reduction in the serum calcium in jaundice, but concluded that the reduction was more apparent than real. Koechig<sup>13</sup> confirmed this work. Walters and Bowler,<sup>14</sup> Snell, Greene and Rowntree,<sup>15</sup> and Zimmerman<sup>16</sup> found no change in the serum calcium, either in obstructive or in other forms of jaundice.

Following the development of methods for estimating the diffusible fraction of the serum calcium it was felt that perhaps the deficiency of this substance accounted for the bleeding. Kirk and King<sup>17</sup> reported moderate reductions in the total calcium with a much greater decrease in the diffusible fraction. They emphasized the importance of diffusible calcium in the clotting complex. Emerson<sup>18</sup> corroborated their observations and drew attention to possible errors due to ether anesthesia. Buchbinder and Kern,<sup>19</sup> on the other hand, found no alteration in the serum calcium after ligation of the common duct in adult dogs, although they did find a progressive decrease of this substance in puppies. Gunther and Greenberg<sup>20</sup> substantiated this work and stated that there was no proof of a deficiency of available calcium in the blood serum of jaundiced patients. It is true that they found the concentration of nondiffusible calcium low in a few instances, but this was accounted for by a lowered concentration of serum albumin. They materially advanced the entire subject by concluding that factors other than a deficiency in calcium must be sought as an explanation of the tendency to bleeding in obstructive jaundice.

12. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: Calcium in the Blood in Tuberculosis, *J. A. M. A.* **68**:1309 (May 5) 1917.

13. Koechig, I.: *J. Lab. & Clin. Med.* **9**:679 (July) 1924.

14. Walters, W., and Bowler, J. P.: *Surg., Gynec. & Obst.* **39**:200 (Aug.) 1924.

15. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Disease of the Liver: II. A Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, *Arch. Int. Med.* **36**:273 (Aug.) 1925.

16. Zimmerman, L. M.: *Am. J. M. Sc.* **174**:379 (Sept.) 1927.

17. Kirk, P. L., and King, C. G.: *J. Lab. & Clin. Med.* **11**:928 (July) 1926.

18. Emerson, W. C.: *J. Lab. & Clin. Med.* **14**:122 (Nov.) 1928.

19. Buchbinder, W. C., and Kern, R.: Experimental Obstructive Jaundice: II. Modification of the Parathyroid Tetany Mechanism in Jaundice, *Arch. Int. Med.* **41**:754 (May) 1928.

20. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch. Int. Med.* **45**:983 (June) 1930.



With the theory of calcium deficiency excluded, the attention of workers was directed toward possible changes in fibrinogen. The suspicion was reasonable, for Howe,<sup>21</sup> Mann and Bollman,<sup>22</sup> Foster and Whipple,<sup>23</sup> and others had shown the liver to be the main source and possibly the only source of fibrinogen, and obstructive jaundice with subsequent damage to the liver could be expected to cause a reduction in the total amount of fibrinogen. On this basis, Full<sup>24</sup> and McLester<sup>25</sup> concluded that the fibrinogen content of the plasma might be used as an index of hepatic function, but Peters and Van Slyke<sup>26</sup> showed that no parallel exists between fibrinogen and the degree of hepatic function, unless the damage to the liver is far more severe than that seen in obstructive jaundice.

Foster and Whipple agreed in finding an increase in fibrinogen following inflammatory and destructive hepatic lesions unless the loss of liver substance was so great that the organ could no longer meet the demands of the body, when a terminal drop occurred. Studies made on the blood fibrinogen in various conditions showed wide variations which were not entirely understood until Wiener and Wiener<sup>27</sup> reported the physiologic limits of the concentration of fibrinogen to be extremely broad. They concluded that any irritation or stimulation of the liver raised the level for fibrinogen, and they found it high during menstruation and pregnancy, following infections, exposure to roentgen ray and ingestion of chloroform and phosphorus, and in early cirrhosis. Gram<sup>28</sup> reported four cases of extreme jaundice from malignant obstruction with extremely high fibrinogen levels.

From a study of the literature we have found that the total fibrinogen increases consistently wherever there has been damage to the tissue, including pregnancy, hemorrhage and infection, with a general rise in malignancy excepting when the liver is radically replaced by metastases.

Moss<sup>29</sup> concluded that in obstructive jaundice there was no deficiency but rather an increase in fibrinogen relative to the extent of damage to the liver. With these results in hand he was forced to con-

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21. Howe, P. E.: *J. Biol. Chem.* **57**:235 (Aug.) 1923.

22. Mann, F. C., and Bollman, J. L.: *Proc. Staff Meet., Mayo Clin.* **4**:328 (Nov.) 1929.

23. Foster, D. P., and Whipple, G. H.: *Am. J. Physiol.* **58**:407, 1922.

24. Full, H.: *Verhandl. d. Kong. f. innere Med.* **33**:201, 1921.

25. McLester, J. S.: *The Diagnostic Value of Blood Fibrin Determinations*, *J. A. M. A.* **79**:17 (July 1) 1922.

26. Peters, J. T., and Van Slyke, D. D.: *Quantitative Chemistry*, Baltimore, Williams & Wilkins Company, 1931.

27. Wiener, H. J., and Wiener, R. E.: *Plasma Proteins*, *Arch. Int. Med.* **46**:236 (Aug.) 1930.

28. Gram, H. C.: *Acta med. Scandinav.* **56**:107, 1922.

29. Moss, Walter: *Experimental Obstructive Jaundice; Its Effect on Fibrinogen and Coagulation of the Blood*, *Arch. Surg.* **26**:1 (Jan.) 1933.

clude that hemorrhage in jaundice was not due to or associated with a deficiency of fibrinogen in the plasma.

Of other clotting components little can be said. The platelets have repeatedly been shown to be within normal limits in these cases. The methods of estimation of thrombin are inaccurate, and although we have extracted thrombin from the clots of jaundiced subjects, there is no quantitative estimation worthy of the name. Howell's<sup>30</sup> claim that a variation in the amount of heparin is the probable cause of bleeding in hemophilia and jaundice is just as uncertain, as there is as yet no quantitative method of determination for heparin.

The importance of dextrose in the clotting complex has been questioned. Partos and Svec<sup>31</sup> showed that substances which increased the coagulability of the blood mobilized glycogen and produced hyperglycemia while substances which prolonged the coagulation time caused hypoglycemia.

Cannon and Gray<sup>32</sup> found that epinephrine increased both the blood sugar and coagulability. Cowan and Wright<sup>33</sup> suggested that this is due to the influence of dextrose in raising the blood calcium. We have found that dextrose will favorably affect persons with jaundice who tend to bleed and that it exercises a protective effect when given preoperatively. The reasons, still obscure, will be discussed later.

Methods for the prognosis of bleeding in obstructive jaundice have been as unsatisfactory as a study of the reasons for bleeding. Ravdin, Riegel and Morrison<sup>34</sup> have agreed with Bancroft, Kugelmass and Stanley-Brown,<sup>35</sup> that coagulation and bleeding times are of no value in determining a tendency to bleeding, and we have found a normal or even shortened coagulation time in the face of fatal hemorrhage.

#### EXPERIMENTAL WORK

Because of the voluminous contradictory literature and previous isolation of various phases of the subject into studies of single elements, we decided to approach the subject of bleeding in obstructive jaundice by making all possible estimations of the formed clotting elements of the blood on the same patients at the same time, and thus experimentally compile the evidence which had previously been accumulated from the literature.

30. Howell, W. H.: *Am. J. Physiol.* **71**:553 (Feb.) 1925; *Bull. Johns Hopkins Ho-p.* **42**:199 (April) 1928.

31. Partos, A., and Svec, F.: *Arch. f. d. ges. Physiol.* **218**:209, 1927.

32. Cannon, W. B., and Gray, Horace: *Am. J. Physiol.* **34**:232, 1914.

33. Cowan, P. W., and Wright, H. N.: *Am. J. Physiol.* **100**:40, 1932.

34. Ravdin, I. S.; Riegel, C., and Morrison, J. L.: *Ann. Surg.* **91**:801 (June) 1930.

35. Bancroft, F. W.; Kugelmass, I. N., and Stanley-Brown, M.: *Ann. Surg.* **91**:101, 1929.

Fourteen patients in the surgical wards were selected for this study. They all had experienced prolonged obstructive jaundice which, with two exceptions, was due either to stones or to tumors. There was one case of biliary cirrhosis and one of arsphenamine poisoning. A few patients had superimposed infections such as cholecystitis and cholangitis. Thirty-five cubic centimeters of blood was taken from each patient, and the coagulation time, icterus index, red cell volume, sedimentation time, fractions for total and diffusible serum calcium and values for fibrin and fibrinogen were determined.

We have regarded the icterus index as the index of progression corresponding roughly to the severity and duration of the disease in these cases. The coagulation time was determined in an 8 mm. tube, after the method of Lee and White.<sup>36</sup> Sedimentation time was determined by placing 0.8 cc. of blood in 0.2 cc. of a 3.8 per cent solution of sodium citrate and recording the time required for the cells to sediment 18 mm.

The determination of fibrinogen was made after the method of Samson<sup>37</sup> with certain modifications. The fibrinogen in citrated plasma was precipitated by the addition of an equal volume of saturated solution of sodium chloride, then packed firmly at the bottom by centrifugation for thirty minutes at 3,000 revolutions per minute, and read directly from calibrated markings on the wall of the tube. While there is some possibility of including other plasma proteins by this method, the fractions, according to Pickering,<sup>38</sup> are thrown down rather independently, and for comparative use the method is quite satisfactory.

The fibrin was coagulated from citrated plasma, as recommended by Gram,<sup>28</sup> by the addition of dilute solutions of calcium chloride and sodium chloride, after which it was thoroughly dehydrated and weighed. Two cubic centimeters of plasma were used for each fibrin determination.

Calcium was determined, after the manner of Gunther and Greenberg,<sup>20</sup> by titration with potassium permanganate. The diffusible fraction was obtained by drawing it through a semipermeable collodion membrane by water suction.

The table shows the results of these determinations on the fourteen patients, tabulated in order from the lowest to the highest icterus index.

*Results of Determinations of Blood Elements on Fourteen Patients*

Number	Icterus Index	Clotting Time in Minutes	Sedimentation Time in Minutes	Diffusible Calcium	Total Calcium	Fibrinogen, Cc. per 5 Cc. Plasma	Fibrin, Gm. per 2 Cc. Plasma
1	2.0	9.0	360	4.600	....	0.30	0.0820
2	15.0	4.5	45	....	9.24	0.60	0.0600
3	17.0	3.5	75	3.022	18.60	0.35	0.0800
4	18.6	4.5	240	7.200	....	0.30	0.0300
5	30.0	7.0	30	4.640	6.33	0.49	0.0420
6	33.0	6.0	15	3.550	8.32	0.60	0.0690
7	40.0	11.0	40	....	6.56	0.70	0.0730
8	45.0	11.0	12	4.350	6.73	0.50	0.0649
9	50.0	17.0	35	....	6.10	0.75	0.0700
10	66.0	2.5	20	3.810	....	0.60	0.0460
11	100.0	25.0	28	2.120	8.45	0.75	0.1110
12	104.0	9.0	28	4.370	8.72	0.55	0.0500
13	143.0	9.0	360	5.280	....	0.15	0.1110
14	150.0	9.0	40	4.640	8.45	0.25	0.1200

36. Lee, R. I., and White, P. D.: *Am. J. M. Sc.* **145**:495, 1913.

37. Samson, K.: *Med. Klin.* **24**:217 (Feb. 10) 1928.

38. Pickering, J. W.: *The Blood Plasma in Health and Disease*, New York, The Macmillan Company, 1928.

The coagulation time was normal for the majority of the patients, although for one it was twenty-five minutes. He bled for three days from a paracentesis abdominis needle wound. The next highest values were twelve and one-half minutes in one case and eleven minutes in two cases. The patient with the twenty-five minute clotting time had a carcinoma of the common duct with ascites. He had been jaundiced for six weeks and had an icterus index of 100. All of the clotting elements were within normal limits.

Values for diffusible calcium were low throughout the group because of the titration method used. Values for total calcium were low except for the patients who were receiving calcium chloride intravenously.

The fibrinogen level increased with the onset of jaundice. The patients with an index of from 50 to 100 who had been jaundiced for from three to six weeks had the highest values. The extremely jaundiced patients with indexes above 100 had values back to normal or below. Relative to this, Schmidt and Brakefield<sup>39</sup> found that bile pigments and acids are excreted in the urine of dogs in maximum amounts approximately two weeks after ligation of the common duct and that from then on the amounts gradually diminish. They attribute this to a decrease in synthesis. Snell, Greene and Rowntree<sup>15</sup> also found an increase of bile acids in the blood to a certain point, then a gradual decrease.

The fibrinogen, especially in the jaundiced patients revealing high values, appeared as a more finely divided precipitate than that in normal blood as though the small particles did not adhere to each other. The values for fibrin varied somewhat but did not show a characteristic change in amount. We did notice, however, that in the cases of deep jaundice the fibrin clots did not retract. They were large, contained a great deal of fluid and were deeply stained. They were less elastic and more easily torn apart than those from normal blood.

#### ANIMAL EXPERIMENTATION

While these observations on patients substantially corroborated the general opinion in the literature, we felt that results would be far more conclusive if they were checked against similar determinations made on carefully controlled laboratory animals.

Dogs were chosen for this purpose as they do well on the average human diet, are large enough to offer little surgical difficulty and have an extrahepatic biliary system quite similar to the human structure. Six animals of average size and mixed breeds were used. After a quarantine period of two weeks, the common

<sup>39</sup> Schmidt, C. L. A., and Brakefield, C. L.: *J. Biol. Chem.* **67**:523 (Feb.) 1925.

bile ducts were severed between double silk sutures near the duodenum. A few accessory ducts were seen and ligated, and on two occasions it was necessary to operate a second time to secure accessory ducts missed at the first entry. Subsequent autopsies showed no ducts which had not been surgically treated.

Excluding one rather old animal which died of pneumonia during the third week, the dogs lived, on an average, for three and a half months after ligation. They went through an initial stage of lethargy and anorexia lasting approximately two weeks. Then they began to take a balanced diet of meat (cooked and raw), milk, rice, potatoes, carrots and bread in generous amounts. They became normally active, taking daily exercise in the open air pens and sleeping in cages in steam-heated rooms at night. They lost weight gradually until about the beginning of

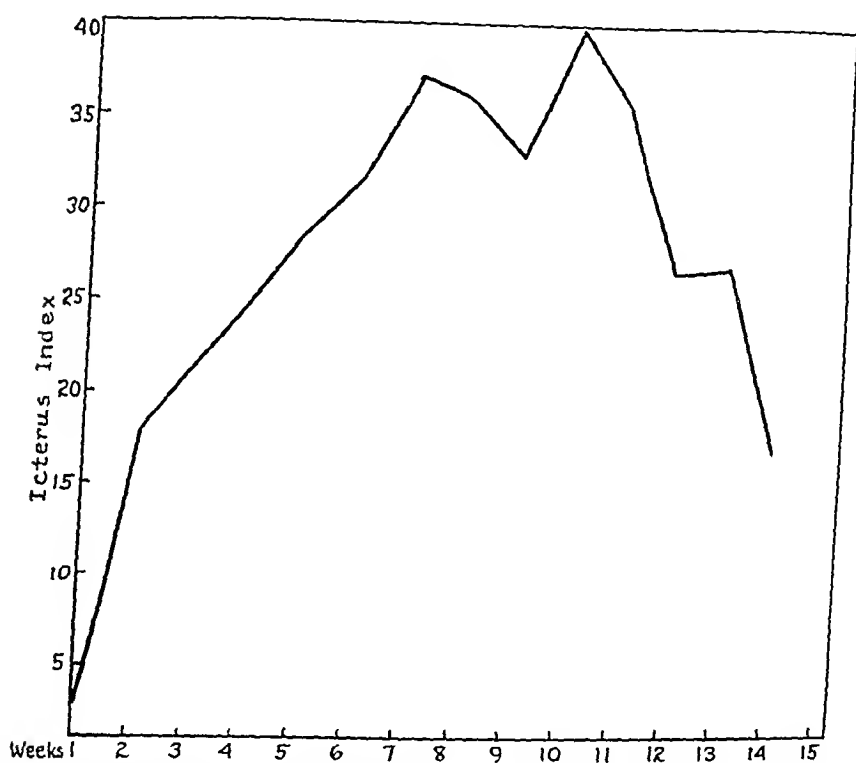


Fig. 1.—Changes in the icterus index in five dogs following ligation of all the excretory bile ducts (composite curve).

the third month, when the loss in weight was accelerated. They again became lethargic and ate little or nothing. Two of the five dogs died of spontaneous hemorrhage into the bowel. One had bleeding into the peritoneal cavity from the liver in the region of the gallbladder. His coagulation time was four and one-half minutes on the day before death. The remaining two apparently died of biliary cirrhosis, characterized by the typical liver, ascites and collateral circulation. Blood was taken from these animals before operation, and determinations were made of the icterus index, coagulation time, sedimentation time, fibrinogen, fibrin, red cell volume, diffusible calcium and total calcium in the manner heretofore described. After operation these observations were made at regular weekly intervals until death (fig. 1). The curves published here are composite averages of the entire group. They coincide with the individual graphs, which are omitted to save space.

The icterus indexes increased rapidly after operation until about the seventh week, when they either became stationary or decreased slightly. Terminally they showed a tendency to decrease rapidly. The stationary period may represent a phase of decreased synthesis or a stage of maximum storage of bile. If a recirculation of bile pigment existed, it is possible that the added synthetic burden placed on the reticulo-endothelial system reached a peak at this time. The final drop occurred for no valid reason, except perhaps a marked terminal decrease in the food intake of the animals.

Hematocrit readings showed an initial drop, presumably from the blood lost at operation, but possibly the change in osmotic pressure of the plasma decreases the individual cell volume (fig. 2). They then remained constant until a final drop occurred from hemorrhage just

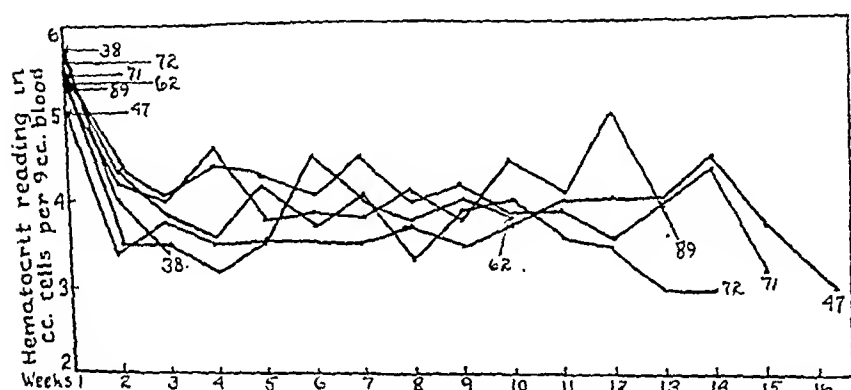


Fig. 2.—Hematocrit readings in five dogs following ligation of the common bile duct.

before death. The animals became dehydrated in the terminal stages, and these constant figures must indicate a loss of red cells, although accurate studies of the blood will have to be reported later.

The coagulation time was not increased beyond normal in any case, but there was a rather constant and significant shortening shortly before death (fig. 3). This terminal change was particularly significant, as will be shown later.

The fibrin revealed no characteristic change in weight, as shown by the curve in figure 4. In the last third of the experimental period, the masses of fibrin were much larger, although they weighed no more after drying. This failure of retraction was constant whether the clots were dried or left in the serum where they formed.

The fibrinogen, although not markedly changed in amount, showed the same inverse ratio to sedimentation as was found in the group of patients. There was an initial rise and then a drop to slightly below normal, where the fibrinogen remained constant (fig. 5 A).

Each specimen of fibrinogen was examined for elasticity and cohesive power by teasing it out on filter paper with glass rods. In the beginning it was an elastic rubbery mass which stretched into thin strands on being torn apart. As time elapsed after the operation, the fibrinogen was observed to sediment much more slowly in the tube; the particles appeared smaller, and after centrifugation there was no elasticity to the mass; it flattened out on filter paper from its own weight and was

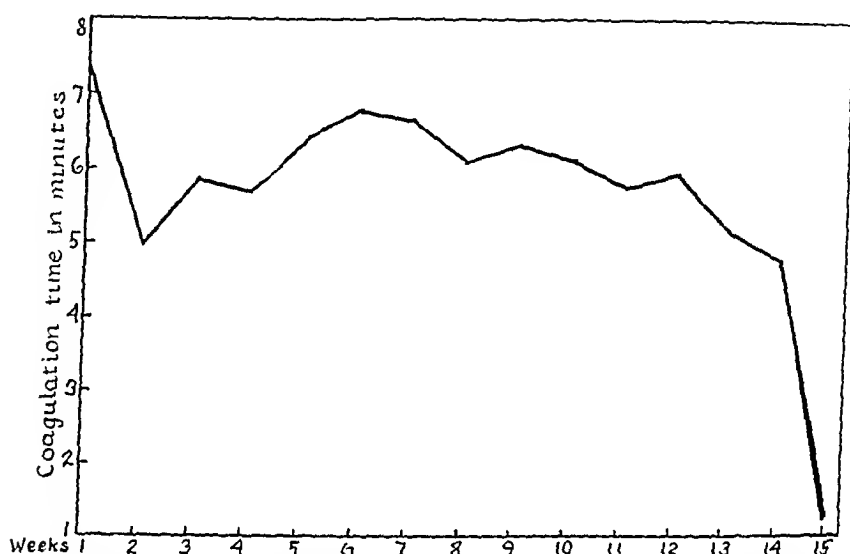


Fig. 3.—Changes in coagulation time in dogs in series 1 (composite curve). The excretory bile ducts were ligated.

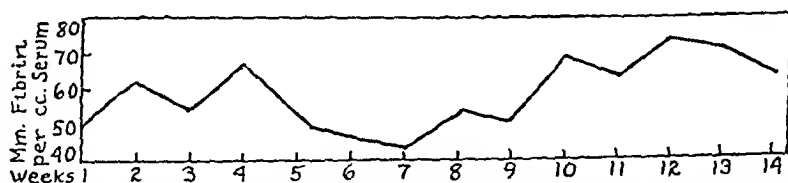


Fig. 4.—Determinations of blood fibrin on five dogs in series 1 with obstructive jaundice (composite curve).

easily torn apart. This change in the consistency of fibrinogen closely followed the nontractility and changes in consistency of the formed fibrin mesh previously described.

Sedimentation time showed an initial rapid drop as low as twelve minutes, then a gradual recovery to about three fourths of the normal time and then a final drop before death (fig. 5 B). The curves in figure 5 were obtained by plotting sedimentation time against elapsed time. This corresponds to the curve obtained for the group of patients and varies inversely with the amount of fibrinogen.

Values for total and diffusible calcium remained fairly constant throughout the experiment (fig. 6). There was no characteristic change in them with the progress of jaundice.

The results of the observations of other writers and our own experience with patients in the hospital and with groups of experimental animals, following ligation of the common duct, show that there is no significant variation in the amounts of the formed clotting elements of the blood; the only important change is the loss of retractile power of the fibrin and whole clot, a shortening of coagulation time shortly

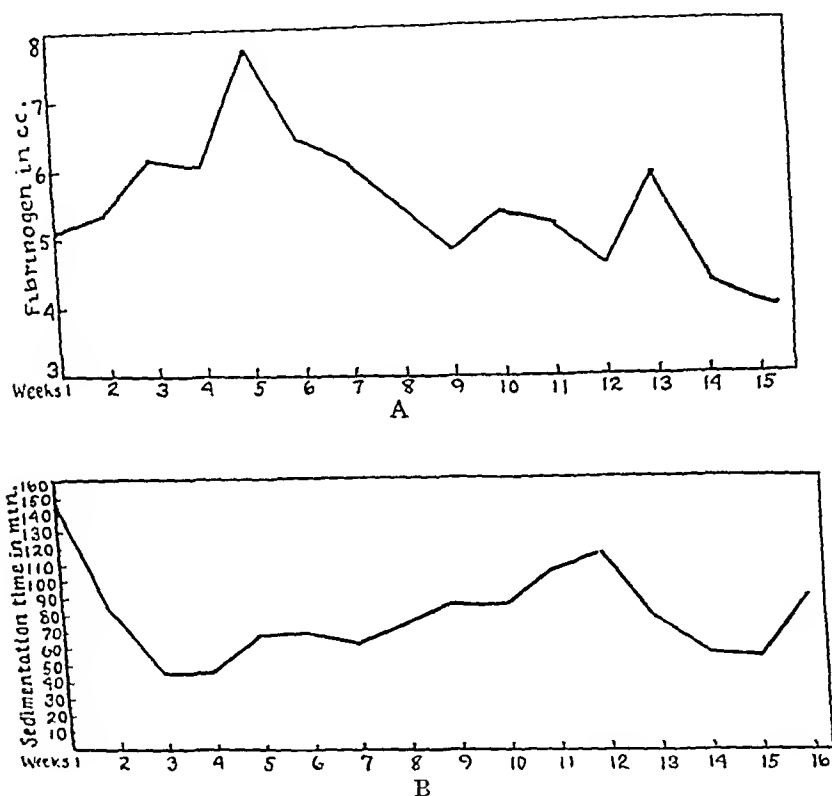


Fig. 5.—A, changes in blood fibrinogen in animals of series 1 following ligation of the excretory bile ducts (composite curve); B, changes in sedimentation time in five dogs after ligation of the excretory bile ducts (composite curve). Note the striking inverse proportion of the curve in A as compared to B.

before death and the imperfect precipitation of an altered fibrinogen in the plasma of these bloods. With these facts it becomes apparent that the error in clotting is due to an additional product which inhibits the process or interferes with the clotting mechanism rather than to an insufficient amount of any of the elements contributing to the normal clotting complex.

Mann has shown that dogs that have undergone hepatectomy die with hypoglycemia. That this is not the only factor in their death,



however, is indicated by the behavior of such animals when given large quantities of dextrose. Instead of dying in the usual time, they manifest a second syndrome closely similar to that of the late stages of obstructive jaundice with jaundice, convulsions, hemorrhage and coma, presumably due to the accumulation in the plasma of split protein products which the liver would normally remove. As cysteine and other mercaptans are excreted by carnivores as taurine in the bile, as well as broken to urea in the liver and converted by the liver to dextrose in small amounts, it was felt that taurine, cysteine and related products are the protein products which most probably back up in the blood and collect in sufficient concentration in the circulating plasma to cause changes in the

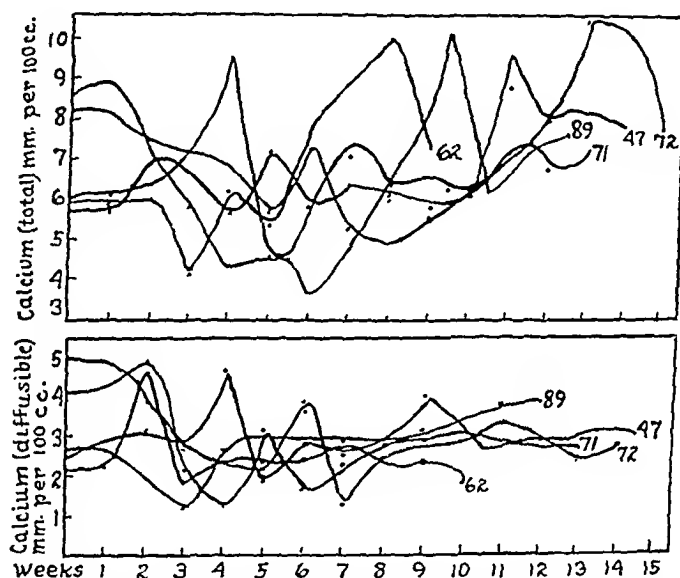


Fig. 6.—Total serum calcium and diffusible calcium in dogs in series 1.

clotting mechanism. Cysteine, glutathione and polyanethylthione have been reported as inhibiting the clotting of blood. Denole and Remert<sup>40</sup> have produced multiple hemorrhages in rabbits by the intravenous injection of polyanethylthione. Mueller and Sturgis<sup>41</sup> have observed that cysteine is an anticoagulant. They placed 0.1 Gm. each of cysteine and of alanine—which is identical except for the mercaptan ( $-SH$ ) radical—in 1 cc. of blood. The blood containing alanine coagulated in ten minutes or less (normal), while that containing cysteine did not clot in twenty-four hours.

We repeated the experiment, using graduated higher dilutions of cysteine up to one containing 0.001 Gm. When present in amounts sufficiently

40. Denole, V., and Remert, M.: *Arch. f. exper. Path. u. Pharmacol.* **158**:211, 1930.

41. Mueller, J. H., and Sturgis, S.: *Science* **75**:140 (Jan. 29) 1932.

minute to allow clots to form, cysteine shortens the coagulation time and changes the normal clot to a dark, friable, nonretractile mass closely resembling the clot formed by the blood of jaundiced dogs shortly before they die of spontaneous hemorrhage. Calcium added to the plasma, both *in vitro* and circulating, temporarily prevents this, while cysteine added to precipitated fibrinogen causes it to swell, forming globoid particles which float. Figure 7 shows the increasing retractile power of the clot as the concentration of cysteine is decreased, the figures under the tubes representing volumes of 10 per cent solution of cysteine hydrochloride.

These facts suggest that cysteine influences blood clotting, affecting both the speed of clot formation and the consistency of the product.

It has been shown that cystine injected into the peripheral circulation can be recovered from other veins shortly afterward in small

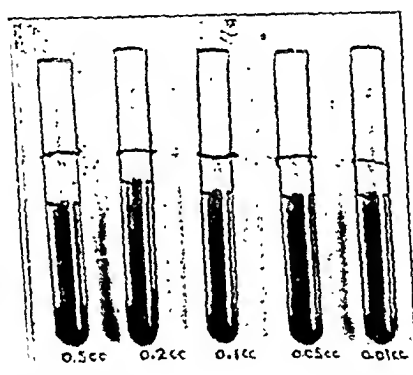


Fig. 7.—Changes in the size of the clot with graduated dilutions of cysteine. Each tube contains 1 cc. of blood. The clot on the left is the largest. It forms almost instantly and is so friable as to flow on tilting the tube. The clot on the extreme right is the most retractile, therefore the smallest, and forms in approximately four minutes. However, it is definitely more friable and forms more rapidly than in unadulterated blood, even though such a minute quantity as 0.001 Gm. of cysteine has been added. The addition of 1 cc. of 2 per cent solution of calcium chloride to each tube prevents these phenomena. When the same dilution of cysteine is produced *in vivo* (calculating blood volume from body weight) in a normal animal, blood withdrawn within ten minutes exhibits a decreased coagulation time and a friable clot.

amounts, but if it is placed in the mesenteric vein none can be recovered, the liver apparently removing it from circulation by a reduction of cystine to cysteine, then through several intermediate compounds such as glutathione (with one molecule of glutamic acid) and polyanethythione. That this is not a simple reaction in the plasma but rather an organic function of the liver is evident because cysteine added to whole blood in the test tube may be recovered many hours afterward.

The normal synthesis of taurine, which is excreted in large amounts by carnivores and man, is thought to start with cysteine. Sulphur, sulphates and thiosulphates have no appreciable effect either on the speed of clotting or on the type of clot formed, the mercaptan radical apparently being the essential influence.

In animals with acute necrosis of the liver after poisoning with carbon tetrachloride the neutral sulphur fraction (which included the mercaptans) of the urine increases. Cystine, tyrosine and leucine are excreted in the urine. Guanidine, with this specific necrosis, is one of the split protein products which apparently collects in excess in the circulation. While it inhibits clotting it does not cause the formation of a poor clot with nonretraction in small amounts, as does cysteine.

If the metabolism and excretion of proteins containing this radical are functions of the liver, the intermediate products, including the mercaptans, must also accumulate in the circulation when excretion through the liver is obstructed by common duct block. From their effects on coagulation *in vitro* it seems reasonable that they would exercise a similar effect when collected in excessive amounts in the circulating plasma.

Normal animals when given larger doses of cysteine hydrochloride intravenously show the same changes in clotting as those with a long-standing biliary obstruction. The clotting time diminishes, and the fibrin mass is spongy and friable and does not retract.

The food source of these products is chiefly meat, and dogs and other carnivores excrete large amounts of taurine in the bile. Human bile contains taurine in moderate amounts, while the excretion from the liver of rabbits, sheep and herbivores generally contains little of this or allied substances.

With the postoperative behavior of dogs with common duct block under normal conditions tentatively established by the group of six animals described, a second group of four was selected, and the common ducts were ligated. To establish the optimum dietary conditions for the production of mercaptan and cysteine, these animals were put on a diet consisting solely of animal protein. The average postoperative survival period of the group was five and a half weeks as compared with thirteen weeks in the group receiving a balanced ration. All of the animals bled badly during the terminal stages of life, the large bowel of each being filled with blood at autopsy. A control animal thrived during this time on the same diet and under the same conditions. Samples of venous blood were taken each week, being collected in sodium citrate under liquid petrolatum which contained no sulphur. In

each of these the Fleming<sup>42</sup> test for cysteine became positive after jaundice had developed and was more strongly positive as the illness progressed, although after the middle of the period the icterus index declined. The Fleming test was not well suited to plasma, however, and after an interval of use Grote's<sup>43</sup> method was substituted and found more applicable. The end-results remained the same. The Grote test was accomplished by withdrawing 1 cc. of plasma from beneath the oil, placing it in a test tube with an excess of powdered sodium bicarbonate and immediately layering 1 cc. of the reagent on it. After fifteen minutes a thin band of violet appears at the junction of the fluids and immediately below a band of green. These bands exhibit a maximum intensity after about one hour, then gradually fade and disappear entirely in twenty-four hours. We divided the results into four groups, negative, 1 +, 2 + and 3 +, depending on the intensity and on the width of the bands. Normal plasma, as well as plasma to which small quantities of bile has been added, produces a negative reaction. In from a week to ten days after ligation of the common duct, the plasma of a dog on a meat diet becomes 1 +. In approximately three weeks it is 2 +, and when the tendency to bleeding is fully developed it is usually 3 +.

While experimentally applying other color tests, we tried therapeutic measures to establish cysteine as an anticoagulant in obstructive jaundice. Clinically, calcium has proved of some value, as it apparently improves the consistency of the clot and has been reported to raise the blood sugar. The intravenous administration of large quantities of dextrose has also been used with some success, and is reported to have raised the blood calcium. This mechanism is not fully understood, but it is known that cysteine may be partially changed to dextrose with the elimination of sulphates and sulphites. Calcium may influence this reaction. Sodium plumbite will convert cysteine to disulphides, but its use is obviously dangerous. Magnesium oxide also breaks the cysteine molecule, causing the formation of an insoluble salt. Ultraviolet rays have been thought to influence cysteine catabolism. We finally selected monobrombenzene as the most useful substance, as it is relatively non-toxic, can be given either orally or intramuscularly, and combines with cysteine to form only mildly toxic bromphenylmercapturic acid and ethereal sulphates which are excreted by the kidneys and which may be isolated from the urine (fig. 8).

Abderhalden and Wertheimer<sup>44</sup> have found that animals given brombenzene excrete moderate amounts of bromphenylmercapturic acid

<sup>42</sup> Fleming, R.: *Biochem. J.* **24**:965, 1930.

<sup>43</sup> Grote, I. W.: *J. Biol. Chem.* **93**:25, 1931.

<sup>44</sup> Abderhalden, E., and Wertheimer, E.: *Ztschr. f. physiol. Chem.* **201**:267, 1931.

when on a pure meat diet, a little of this acid when starved, and practically none when given carbohydrates. Bromphenylmercapturic acid appears in the urine as bundles of needle-like crystals, and the number isolated is a partial index of the relative amounts of cysteine and brombenzene in the circulating blood. The remaining fraction, however, is eliminated as ethereal sulphates, and even with known amounts of both cysteine and brombenzene injected the excretion may be by ethereal sulphates, bromphenylmercapturic acid or both. These crystals, then, do not represent a quantitative test, but only indicate the presence of mercaptan bodies.



Fig. 8.—Crystals of bromphenylmercapturic acid from the urine of a jaundiced animal.

In the hope of eliminating cysteine from jaundiced dogs with this drug, a third group of four dogs was selected; their common ducts were tied as before, and they were placed on a protein diet (fig. 9). Shortly after jaundice appeared they were given 0.1 cc. of brombenzene per kilogram each day by mouth. The same clinical picture developed as in the other dogs on protein feeding, but after from seven to ten days they were much more active and playful. Their postoperative course was protracted, being practically double that of dogs fed protein without brombenzene. They showed no signs of bleeding but died of emaciation, inanition and a moderate degree of hepatic cirrhosis. At autopsy a small amount of blood was found in the terminal bowel of

two animals. One animal in this group received, in addition, ultraviolet irradiation for an hour each day. He not only remained in better condition than the other animals throughout the experiment, but lived longer than any in the group. The urine was collected weekly, acidified, allowed to stand ten days, alkalinized, filtered, redissolved in acid, passed through animal charcoal, taken up with a weak solution of ammonia and evaporated in order to isolate crystals of bromphenylmercapturic acid.<sup>44</sup> These were found early in the stages of jaundice when brombenzene was given, but they did not appear late in the disease. We

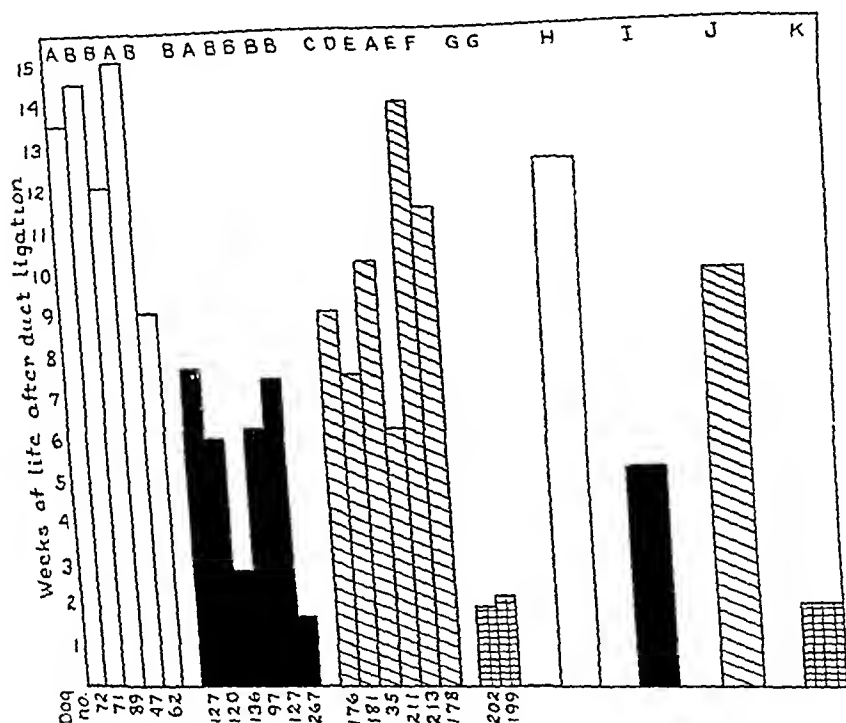


Fig. 9.—Longevity chart of jaundiced dogs. The white areas represent a balanced diet, the black, a meat diet; the oblique lines, a meat diet plus 0.1 cc. of brombenzene daily per kilogram of body weight; the squares, a meat diet plus 0.4 cc. of brombenzene daily per kilogram of body weight. The primary causes of death were as follows: A, cirrhosis; B, hemorrhage; C, undetermined; D, general edema and slight bleeding; E, volvulus; F, cirrhosis and slight bleeding; G, brombenzene poisoning. Charting H to K represents the average duration of life in jaundiced dogs: H, those on a mixed diet; I, those on a meat diet; J, those on a meat diet plus 1 cc. of brombenzene daily per kilogram of body weight; K, those on a meat diet plus 0.4 cc. of brombenzene daily per kilogram of body weight.

attributed this to the fact that the synthesis of bromphenylmercapturic acid, a function of the liver, was inhibited by blockage of bile, and that the intermediate ethereal sulphates only were synthesized.

The Grote test was positive in each animal but did not reach the intensity shown in the untreated dogs. The maximum intensity corresponded to 1 + or 2 +.

Figure 10 shows an animal at the end of three months after ligation of the duct. During this time he had been given a meat diet with 0.1 cc. of brombenzene per kilogram of body weight. He showed emaciation from extreme toxicity but no tendency to bleed.

While brombenzene in large doses produces the same toxic lesions as other benzene compounds, the doses used here have caused no apparent histopathologic changes or physiochemical reactions other than those mentioned. Complete studies of the changes in the tissue and in the blood in obstructive jaundice, cysteine intoxication and brombenzene poisoning will be reported later.



Fig. 10.—Dog at the end of three months after ligation of the duct during which time he had received a meat diet with 0.1 cc. of brombenzene per kilogram of body weight.

#### COMMENT

With the experience of other investigators and the results of our own work before use, it seems that the hemorrhage which follows prolonged obstructive jaundice is not due to quantitative deficiency in the measurable formed clotting elements of the blood, but rather to an addition of some inhibiting substance which changes the quality of the fibrinogen, fibrin and whole clot. This substance does not, as was popularly supposed, always prolong the coagulation time, for we have found consistently normal or short coagulation time in practically all of the hospitalized patients and experimental animals. Furthermore, the hemorrhage in these subjects is not a massive and sudden exsanguination, but rather a slow consistent oozing which over a period of hours results in serious loss of blood. This slow type of bleeding is most commonly observed in experimental animals in whom small amounts of blood start to ooze into the gastro-intestinal tract through

the mucosa for sometimes from eight to ten days before fatal hemorrhage occurs. This is also occasionally seen in hospitalized patients, but of course in them bleeding occurs more often following operations on the extrahepatic biliary system. The bleeding in these types, however, is similar and is a slow oozing type of exsanguination rather than an acute hemorrhage. The influence of operation in inducing this bleeding is apparently important, for patients and experimental animals that would not have bled otherwise bleed when channels of the circulatory system are artificially opened. The effects of damage to the tissues during operation and of anesthesia on this bleeding are apparently also contributory. Whether these effects are due to an introduction of added intermediate products of protein metabolism into the circulating plasma because of inhibited hepatic excretion, or to a reduction of the efficiency of hepatic metabolism, we are not prepared to say, but it is probable that both occur.

The mechanism of bleeding, as we have observed it, both in vitro with the addition of cysteine to normal blood and in vivo by injecting cysteine into normal animals and by inducing a collection of metabolites by ligation of the common duct, is one of seepage through an inefficient clot. As previously stated, the blood clots as rapidly or more rapidly than normal. The clot which is formed, however, is influenced by the collected intermediate products of protein metabolism, and, instead of forming a strong type of occluding mesh which retracts and efficiently prevents the escape of blood, a porous, nonretractile, friable gel of poor consistency is precipitated which is not capable of obstructing the flow of blood and through which both cells and plasma pass slowly. This is most evident after the initial retraction of very small vessels has relaxed. Cysteine and the related forms of mercaptan have this ability to influence the plasma and clotting elements, and that they do collect in excessive amounts in obstructive jaundice may be adequately demonstrated by colorimetric reactions. This theory is further strengthened by the behavior of subjects with such obstructions when brombenzene medication is used, and its effect in improving the clotting mechanism is interesting and definite. It is evident, however, that the animals fed suitable amounts of brombenzene are not protected to any extent from the toxic effects of cholemia but that their longer period of survival is due to the fact that they do not bleed.

Last, but quite important, is the fact that protein diets are apparently badly suited to subjects with biliary obstruction, and that high amounts of carbohydrates are beneficial. We have not yet had an opportunity to carry out this preoperative regimen on patients with obstructive jaundice who are about to be operated on, but we hope to report this procedure in connection with a number of operative cases at a later date.



## CONCLUSIONS

1. There is no important quantitative change in the formed clotting elements in obstructive jaundice, but the quality of fibrinogen and fibrin is definitely altered.
2. The contention that sedimentation time is an index to clotting power is not substantiated.
3. The sedimentation time appears to vary inversely as the amount of fibrinogen.
4. The clotting time is normal or shortened, with few exceptions, and is not a reliable index to clotting power.
5. The clot formed is large, friable and nonretractile.
6. The cause of this clotting deficiency is the accumulation of incompletely metabolized products of proteins in the blood.
7. These products are sulphur-containing compounds, probably cysteine and its related mercaptans.
8. The use of brombenzene effectively reduces the amount of circulating cysteine and definitely reduces the bleeding tendency in experimental animals.

# ATLANTO-EPISTROPHEAL SUBLUXATIONS

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NEW YORK

Subluxations of the cervical vertebrae were first described in this country in 1889 by Walton,<sup>1</sup> who devised the method of manipulative reduction that bears his name. In 1907 Corner<sup>2</sup> reported twenty cases of atlanto-epistropheal subluxations and dislocations, all of traumatic origin, and gave what is probably the best account of the mechanism of their production. The first report of a case of distention subluxation, i. e., subluxation probably due to effusion in the joints concerned, was made by Jacobs<sup>3</sup> in 1916. In 1932 Watson Jones<sup>4</sup> reviewed fourteen cases from the literature and reported two personal cases. The present paper is based on a consideration of twenty cases of distention subluxation and ten cases of related conditions observed from 1923 to 1933 at the New York Orthopaedic Dispensary and Hospital.

## ANATOMIC CONSIDERATIONS

The atlas and epistropheus articulate through four joints: the atlantodental joint between the anterior atlantal arch and the dens epistrophei; the transversodental joint between the transverse ligament and the dens, and the two joints between the lateral masses.<sup>5</sup> Often the synovial cavities of all four joints communicate with each other and with the atlanto-occipital articulations. When this monocele type of synovial cavity is present inflammatory processes or effusions in one joint have free access to the other joints.

The joints drain into the retropharyngeal glands, into which the nasopharynx also drains. The efferent vessels of these glands drain into the deep cervical chain, as do the tonsil, the middle ear, the teeth and the nose. A pathway to the joints is thus suggested from foci about the head and neck. The second cervical nerve runs for a portion of its course in the capsule of the atlanto-epistropheal joint, which offers a probable explanation of occipital neuralgia in many cases in which this joint is affected.

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\* Fellow of the New York Orthopaedic Dispensary and Hospital.

1. Walton, G. L.: Boston M. & S. J. **120**:277, 1889.

2. Corner, E. S.: Rotary Dislocations of the Atlas, *Ann. Surg.* **45**:7, 1907.

3. Jacobs, C. M.: Atlas and Axis Luxation, *Am. J. Orth. Surg.* **16**:357, 1916.

4. Jones, R. Watson: Spontaneous Hyperaemic Dislocation of the Atlas, *Proc. Roy. Soc. Med.* **25**:58, 1932.

5. Poirier, P., and Charpey, A.: *Traité d'anatomie humaine*, Paris, Masson & Co., 1924, vol. 1, p. 74.

The opposed articulating surfaces of the lateral masses are both convex. When denuded of cartilage the inferior facets of the atlas are slightly concave. In vivo, however, this concavity becomes a convexity by virtue of the greater thickness of the cartilage in the middle (1.5 mm.) as compared with that in the periphery (0.5 mm.). A similar distribution of the cartilage increases the convexity of the superior articular surfaces of the epistropheus. Hence, when the articulation is examined from its lateral aspect it resembles the end-views of the hulls of two boats placed keel to keel. The anterior and posterior spaces, where the surfaces of the two joints do not come into contact, are occupied by a fringe of synovial membrane. When the atlas is fully rotated on the epistropheus, and only the peripheral part of the articular cartilages are in contact, the cervical portion of the spine loses from 2 to 3 mm. in height. This arrangement allows a shorter capsule to serve

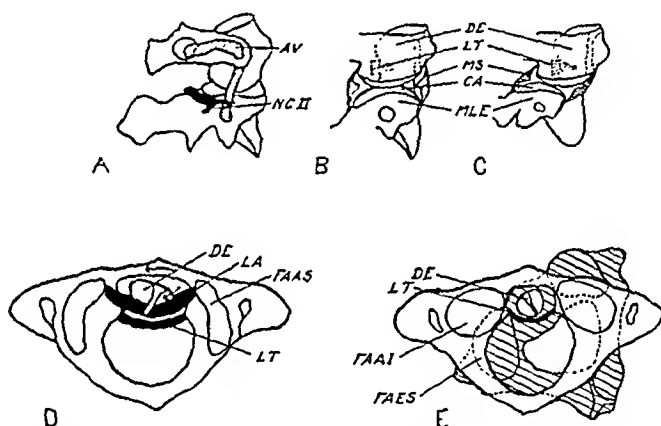


Fig. 1.—*A*, lateral view of the atlas and epistropheus; *B*, lateral view looking directly into the atlanto-epistropheal joint; *C*, same as *B*, with the epistropheus rotated; *D*, superior view of the atlas and dens; *E*, superior view of the atlas and epistropheus with rotation of the epistropheus. The contiguous surfaces of the joints are represented. The drawings are diagrammatic: *AV*, vertebral artery; *NCII*, second cervical nerve; *DE*, dens; *LT*, transverse ligament; *MS*, synovial membrane; *CA*, articular cartilage; *MLE*, lateral mass of the epistropheus; *LA*, alar ligament; *FAAS*, superior articular surface of the atlas; *FAAI*, inferior articular surface of the atlas; *FAES*, superior articular surface of the epistropheus.

the joint. The synovial fringes in the joint, when inflamed or adherent, may conceivably be an obstacle to the reduction of a subluxation or to free motion in an unluxated joint. Possibly these fringes are responsible for the nuchal crepitus elicited on rotation in most cases of rheumatoid arthritis.

The anterior atlantal arch is maintained in close apposition to the dens in all positions by a strong, thick, fibrous band, the transverse ligament, which passes between two tubercles prominently situated in the middle of the internal aspect of each atlantal lateral mass. The total

thickness of the cartilage of the atlantodental joint is from 1 to 1.3 mm. When the atlantodental interval is greater than this distance, there is a corresponding stretching or relaxation of the transverse ligament.

Movements of rotation at the atlanto-epistropheal joint are checked mainly by the alar ligaments, attached to the posterolateral portion of the head of the dens, running laterally and superiorly to the internal aspect of the occipital condyles. Figure 1 *D* illustrates how, as the atlas rotates to the left about the vertical axis of the dens, the right alar ligament becomes taut toward the limit of rotation and causes the head to be tilted to the right. This mechanism explains how rotation of the head is accomplished much more easily when accompanied by tilt in the opposite direction and why this tilt is present in rotation deformities.

The upper cervical vertebral foramina are relatively large to allow for the narrowing of the neural canal that occurs with rotation. In the average adult the dimensions of the vertebral foramen of the atlas are 30 mm. transversely and 25 mm. sagittally; of the epistropheus, 25 and

TABLE 1.—*Mobility of Different Portions of the Cervical Spine*

	Flexion and Extension (Total), Mm.	Lateral (to Each Side), Mm.	Rotary (to Each Side), Mm.
Atlanto-occipital.....	20 to 50	7 to 20	0
Average.....	30	10	
Atlanto-epistropheal.....	10	4	40
Remainder of cervical spine (5 joints).....	30	30	40

19 mm.; and of the third cervical vertebra, 23 and 15 mm. The cord is 10 mm. in diameter in this region.

Table 1 showing the mobility of the different portions of the cervical spine is based on the textbook on anatomy by Poirier and Charpey,<sup>5</sup> confirmed by roentgenographic studies of my neck and clinical observations. The mobility is somewhat greater in children and is less in older subjects. Rotation is decreased in hyperextension and hyperflexion and is increased in slight flexion. Since there is no rotary mobility between the head and the atlas they rotate as a unit.

#### MECHANISM OF SUBLUXATION

A distinction must be made between subluxation of the atlas on the epistropheus and rotation deformity occurring in the atlanto-epistropheal joint. With a simple rotation deformity the transverse ligament is not relaxed, and there is no slipping forward of the atlas on the epistropheus. However, the rotation of the atlas on the epistropheus is fixed and necessitates a compensatory rotation in the lower part of the cervical spine to bring the head to the neutral rotary position. There are usually

tilt and flexion, along with rotation, deformities. Rotation deformity represents fixation in a position possible to a normal neck.

Subluxation implies relaxation or stretching of the transverse ligament and the slipping forward of the atlas on the epistropheus. Between these vertebrae is normally 10 degrees of flexion extension mobility, accomplished by a rocking motion of the convex surfaces of the joints on each other. The transverse ligament prevents any forward gliding of the atlas. With relaxation of the ligament, however, one or both of

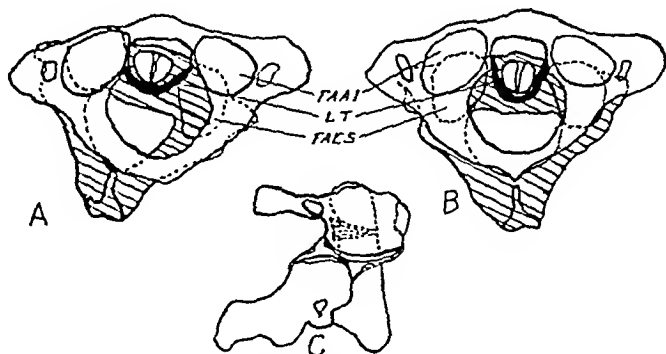


Fig. 2.—*A*, unilateral subluxation of the atlas; *B*, bilateral subluxation of the atlas; *C*, lateral view of the atlas and epistropheus showing subluxation of the atlas with flexion. The drawings are diagrammatic.

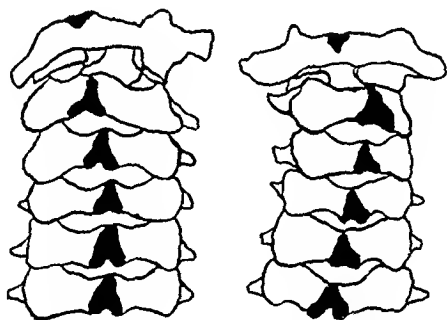


Fig. 3.—Diagrams of the cervical vertebrae viewed posteriorly in a normal rotation to the right and in right rotation deformity. In the latter the head and atlas are brought to the midline through a rotation of the cervical vertebrae to the left from the second segment downward.

the atlantal lateral masses may slip forward on the epistropheus. Flexion of the atlas on the epistropheus usually accompanies this subluxation. If the subluxation is unilateral or predominantly on one side rotation deformity is also present.

Complete dislocation of one or both atlantal lateral masses is impossible without dangerous narrowing of the neural canal, unless there is associated fracture of the dens. An examination of an articulated atlas and epistropheus reveals that in order for dislocation to occur when

both the dens and the transverse ligament are intact, 65 degrees of rotation is necessary. In the adult the neural canal is thereby narrowed to a diameter of 7 mm. If the transverse ligament is relaxed sufficiently to allow a forward subluxation of 5 mm., a complete dislocation of one lateral mass can take place with 45 degrees of rotation, the neural canal being thereby narrowed to a diameter of 12 mm. All the observed forward subluxations of more than 5 mm. were bilateral. With an intact dens a complete bilateral forward dislocation obliterates the neural canal altogether.

Posterior subluxation of the atlas as a whole is manifestly impossible without fracture of the dens or of the anterior arch of the atlas. If the transverse ligament is not relaxed any rotation forward on one side results in a corresponding rotation posteriorly on the other.

When the head becomes fixed in a position of rotation through the atlanto-epistropheal joint, with or without subluxation forward, the subject attempts to bring the head to a position of "eyes front" by rotating through the lower cervical joints in a direction opposite to the rotation deformity. Each of the vertebrae can rotate about 8 degrees to either side. The compensatory rotation occurs from the second cervical vertebra down, that is, the second presents the maximum rotary deviation, the lower vertebrae successively approaching the neutral position. The spines of the cervical vertebrae thus rotated deviate to the side of the midline toward which the head is turned, which is the reverse of what occurs when the head is turned on a normal neck (fig. 3).

A similar mechanism produces lordosis of the lower cervical spine to compensate for the flexion component of the deformity when that is marked.

#### ROENTGENOGRAPHIC OBSERVATIONS

The lateral and anteroposterior views referred to in this section signify roentgenograms centered on the atlas, using the following technic: a lateral view centered just below a line through the tips of the mastoid processes, and an anteroposterior view taken through the wide-open mouth centered along a line connecting the upper teeth and the occipital protuberance.

*Lateral View.*—1. Increased Anterior Atlantodental Interval: This sign is pathognomonic of forward subluxation of the atlas, and its extent and persistence are important in judging the progress of the condition and in making a prognosis. Forward displacement is gaged by the distance between the anterior border of the dens and the ring shadow which marks the anterior arch of the atlas. Normally this interval should not be more than from 1 to 2 mm.

2. Swelling of Soft Tissue: The depth of the shadow of the soft tissue anterior to the first two cervical vertebrae should normally be

equal to that of the shadow of the soft tissue anterior to the other cervical bodies. Thickening of this shadow in subluxated or deformed cervical vertebrae indicates active inflammation and suggests the need of functional rest for the neck.

3. Flexion of the First on the Second Cervical Vertebra: The line joining the inferior borders of the anterior and posterior arches of the atlas and the line joining the inferior borders of the articular processes of the epistropheus with the inferior border of its spinous process should be parallel or converge posteriorly when the head is in the neutral position. With the head flexed these lines may normally



Fig. 4.—Lateral view of the atlantal region in a case of subluxation. Flexion of the atlas is not present. The anteroposterior view taken at the same time showed no overlapping. Note the increased anterior atlantodental interval, the shadow of the soft tissue anterior to the vertebral bodies, the rotation of the second and third cervical vertebrae and the slight lordosis.

converge anteriorly at an angle as great as 10 degrees. In cases of subluxation and rotary deformity of the first on the second cervical vertebra the atlas is usually somewhat flexed on the epistropheus. In only two cases in this study was hyperextension present. If a true lateral view of the atlas is not obtained it is difficult to determine the degree of flexion.

4. Compensatory Lordosis of the Lower Cervical Vertebrae: This sign is present when the flexion of the first on the second cervical vertebra is marked, usually in cases of severe bilateral forward subluxation.

5. Failure of the Two Halves of the Posterior Arch of the Atlas to be Superimposed: In a true lateral view the two sides of the posterior arch are superimposed. Since there is lateral tilt deformity in cases of unilateral forward subluxation, and often in simple rotation deformity, lateral roentgenograms taken at right angles to the neck rather than to the atlas will show both sides of the posterior arch.

6. Evidence of Rotation of the Cervical Vertebrae from the Second Vertebra Downward: This is seen in the presence of rotation deformity between the atlas and epistropheus. The joint spaces of the lateral articulations of the two sides are no longer superimposed, but their shadows are projected, one anterior to the other.

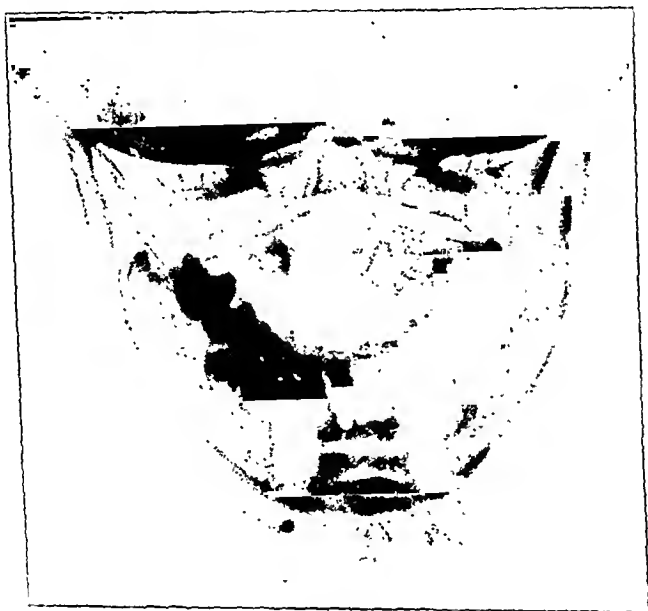


Fig. 5.—Anteroposterior roentgenogram of the atlantal region. Note: the deviation of the chin and the spine of the epistropheus to the same side of the midline; overlapping on the side of the forward movement of the atlas; the apparent lateral displacement of the atlas. That the displacement is only apparent is evidenced by the symmetry of the atlantal lateral masses about the dens.

7. Diminished Anteroposterior Diameter of the Atlantal Vertebral Foramen: George and Leonard<sup>6</sup> in their work on roentgenography of the spine stress the importance of diminished width of the atlantal vertebral foramen in a diagnosis of forward subluxation of the atlas. This sign is open to much misinterpretation, since rotation of any part of the cervical spine gives rise to foreshortening, which simulates diminished width of the foramen.

<sup>6</sup> George, A. W., and Leonard, R. D.: *The Vertebrae Roentgenologically Considered*, volume 8 of *Annals of Roentgenology: A Series of Monographic Atlases*, edited by James T. Case, New York, Paul B. Hoeber, Inc., 1929, p. 81.



*Anteroposterior View.*—1. Lateral Deviation of the Epistropheal Spine: This is the most important sign to be looked for in the anteroposterior view. The shadow of the spine has the form of an inverted V and is readily identified. When normal cervical vertebrae in a position of rotation are roentgenographed in the sagittal plane of the head, the shadows of the spines of the vertebrae are successively farther from the midline. If, however, there is rotation deformity of the head, with or without forward subluxation, the spine of the second cervical vertebra is found on the same side of the midline as the direction of rotation, while the spines of the lower cervical vertebrae are successively nearer the midline. The reason for this deviation to the side toward which the head is turned has been previously referred to: The lower cervical vertebrae, in an attempt to enable the patient to look straight ahead, rotate in a direction opposite to that of the rotation deformity. The amount of rotation present between the atlas and epistropheus can be estimated. If the spine of the second cervical vertebra is in line with the lateral margin of the dens the amount of rotation is 15 degrees; if with the transverse process of the atlas, 50 degrees.

2. Overlapping of the Shadow of the Lateral Masses of the First and Second Cervical Vertebrae on One or Both Sides: As indicated in the mechanism of subluxation, this sign is rarely due to the complete downward and forward dislocation of one lateral mass of the atlas on the epistropheus. Bilateral overlapping is often seen, but a bilateral dislocation with an intact dens is incompatible with life. The two factors that produce the appearance of overlapping are flexion of the atlas on the epistropheus and a forward or backward position of one or both lateral masses of the atlas, due either to rotation or to subluxation forward. Both of these factors were present in every case in this series showing overlapping in the anteroposterior view. An appearance of overlapping can be obtained if a roentgenogram is taken with the head flexed and rotated. This was true of my neck, and an appearance of overlapping of the lateral masses on one side was obtained. Furthermore, three cases in this series without forward displacement of the atlas showed overlapping. On the other hand, three cases showing forward displacement of the atlas did not present overlapping. In several other cases the overlapping originally present was absent in subsequent roentgenograms while the forward displacement remained.

In two cases in this series the anteroposterior roentgenogram represented the lateral mass of the atlas which was rotated posteriorly as overlapping the corresponding lateral mass of the epistropheus; e. g., in two roentgenograms of one patient taken on the same morning, with no change in the deformity, overlapping was present on one side only in each roentgenogram, but on opposite sides. This fact suggests that the side on which the overlapping appears depends on the variation in the

direction of the projection of the rays through the spaces of the joints. When the roentgen rays are projected from a point inferior to that employed in the usual technic it is on the posteriorly rotated side that overlapping is seen.

To sum up, overlapping is an appearance occurring with flexion and rotation of the first on the second cervical vertebra. It is not pathognomonic of subluxation or of the side on which the forward movement has taken place.

3. Lateral Displacement of the Atlas: This sign is subject to many errors of interpretation. The first cervical vertebra has a normal lateral mobility on the second as great as that seen in roentgenograms of most subluxations. Moreover, whenever rotation is present the second cervical vertebra is foreshortened in the anteroposterior view, giving the appearance of lateral displacement to one or both sides. In order to give significance to this appearance of lateral displacement the head must be held erect on the spine and both lateral masses must be displaced laterally with respect to the dens. Under these conditions a unilateral displacement represents a pathologic fixation in a position within the normal range of motion. A bilateral displacement of the atlantal lateral masses in opposite directions, however, indicates the fracture of one of the arches of the atlas.

Decalcification of the upper cervical vertebrae, emphasized by Jones,<sup>4</sup> was not found in any case in this series. The only pathognomonic sign of subluxation in the absence of a fracture is an increased anterior atlantodental interval in the lateral view of the atlas.

#### ETIOLOGY

An etiologic classification of the subluxations and rotation deformities studied divides them into three groups: (1) secondary to distention of the joints with relaxation of the transverse ligament, twenty cases; (2) traumatic, nine; (3) resulting from poliomyelitis, one.

*Distention Subluxations.*—The age distribution in this group was: between 5 and 10 years, eight; between 10 and 15 years, seven; between 15 and 20 years, two; 20 years and over, three.

As a rule the patients were pale, undernourished and sickly. Eleven of the twenty patients had rheumatic fever; two of these died of it while under observation. Fifteen patients, eight of whom had rheumatism, had inflammatory processes about the head and neck shortly before the onset of symptoms of subluxation. The inflammatory conditions which occurred were tonsillitis, mastoiditis, cervical abscess, osteomyelitis of the lower cervical vertebrae, acute dental infection, chronic coryza and influenza. Eight of these patients had operations shortly before the onset of symptoms. It has been thought that twisting of the head while

a patient is under anesthesia might produce a subluxation. However, in half the cases the onset of symptoms was a day or more after the operation and was gradual and progressive. Furthermore, no subluxations were observed following any other type of operation than those for an inflammatory process in the head or neck. The operations performed were mastoidectomy, tonsillectomy, incision and drainage of a cervical abscess and removal of tuberculous glands of the neck (followed by suppuration).

The following hypothesis is advanced to explain the occurrence of distention subluxations: The synovial membrane of the atlanto-epistropheal joints responds either to a generalized attack of rheumatic fever or to infection carried through the lymphatics or by continuity from infectious processes about the head or neck. This response to infection occurs most readily in persons who have had rheumatic fever. The joint between the dens and the transverse ligament is simultaneously affected, possibly because it often communicates with the other joints of the articulation. The transverse ligament relaxes and permits forward displacement of the atlas on one or both sides.

*Traumatic Conditions.*—Rotation deformities without subluxation were occasioned most frequently by trivial traumas, such as falling out of bed or turning the head suddenly. Overcorrection of congenital torticollis, with immobilization in plaster following myotomy, was responsible for two cases. The condition is probably analogous to sprain. In no case in this series did trauma alone precede forward subluxation. In two cases fracture of one of the atlantal arches with lateral subluxation of the lateral masses resulted from forces applied suddenly to the top of the head. One patient was buried in a cave-in; the other struck the bottom of a swimming pool when diving.

*Poliomyelitic Subluxation.*—Paralysis of the stabilizing muscles of one side of the neck gave rise in one case to true subluxation of the atlas with relaxation of the transverse ligament.

#### SYMPTOMS

Subluxation and simple rotation deformities of the atlanto-occipital joint present a similar symptomatology. The chief complaint was most often of stiffness, frequently of deformity or pain on motion. These three symptoms were always present to some degree. Rarely, and only in the severer cases, were difficulty in opening the mouth, dysphagia and changes in the voice complained of. Three patients with bilateral subluxation had neurologic symptoms due to pressure on the cord. Occipital headache was recorded three times.

Difficulty in opening the mouth is associated with, and is probably due to, extreme flexion of the head on the neck in marked subluxations

Swallowing becomes difficult apparently because of the obstruction offered to the rising of the glottis by the flexion of the head and the protrusion of the second, third and fourth cervical vertebrae into the pharynx as they hyperextend to compensate for the flexion deformity in the atlanto-epistropheal joint.

#### SIGNS

The head is held stiffly in flexion with the chin close to the neck. When rotation deformity is present in addition to flexion the head is held tilted toward, and rotated away from, the side on which the atlas has moved forward. The patient appears to be straining to bring the head to the midline. On arising from the prone position, the head is supported by the hands. Instead of turning the head, the whole body is turned.

The spine of the second cervical vertebra is palpated on the side toward which the head is turned, i. e., opposite the side on which the atlas has moved forward. The mechanism of this phenomenon has been previously referred to. The paraspinal muscles stand out prominently on the side toward which the epistropheal spine is deviated and are usually in spasm. A colleague described a case in which this spastic muscular mass was mistaken for an abscess. The patient died during attempted drainage. If the subluxation is symmetrically bilateral the spine of the epistropheus is not rotated, but becomes more prominent in the midline. The soft tissues in the region of the subluxation are tender, particularly over the bony prominences.

Mobility is extremely limited by spasm. Attempts at motion cause pain, usually localized just below the mastoid processes. In the supine position, with the head supported on the table, the mobility is often much greater, probably because the stretched transverse ligament is no longer under tension. Even when lying down it is usually impossible to rotate the head past the midline toward the side on which the atlas has moved forward.

When rotation deformity is present, examination of the pharynx reveals a bulging on the side opposite that on which the atlas has moved forward. This is caused by the rotation of the cervical vertebrae below the first (previously referred to).

The neural canal is narrowed in proportion to the amount of forward subluxation of the atlas. In five patients the subluxation was over 10 mm. Three patients with subluxation of 11, 12 and 14 mm., respectively, had signs of pressure on the cord. On the other hand, two patients with subluxations of 12 and 13 mm., respectively, did not have pressure on the cord.

The heart should always be examined in view of the high incidence of rheumatic fever in this group.

## DIAGNOSIS

An acquired torticollis with spasm of the muscles should at once arouse suspicion of subluxation or rotation deformity at the atlanto-epistropheal joint. A history of rheumatic fever, infection about the head or neck or trauma antecedent to the onset of the symptoms is still more suggestive. Final diagnosis should be made by roentgenogram.

Differential diagnosis should distinguish the condition from congenital torticollis, specific or nonspecific arthritis of the cervical spine (a subluxation may develop later on an arthritic basis), myositis and fibrositis of the neck, spasmodic torticollis, osteomyelitis of the cervical vertebrae and subluxations of the lower cervical vertebrae (particularly following trauma).

## TREATMENT

The aim of treatment in these conditions is twofold: (1) reposition of the bones concerned in their normal relationship and (2) restoration of the inflamed or damaged structures of the joint to a healthy state.

From the therapeutic point of view the cases studied can be divided into four groups: distention subluxation; simple rotation deformity; fracture of the atlas, and poliomyelitic subluxation.

*Distention Subluxation.*—Of the twenty cases in the group reduction was attempted in fourteen. The methods employed were traction and manipulation, of the Walton type, i. e., tilt, then rotation opposite to the deformity, with fixation in a plaster cast for from four to twenty weeks. Traction consisted of: (1) straight traction on the head in bed; (2) strong traction on the head with pelvic countertraction, followed by support in a plaster cast; (3) a plaster cast applied while the head is under traction, and (4) suspension with manipulation.

No permanent reduction of the forward displacement was obtained under treatment except in one instance. Strong traction on the head with pelvic countertraction followed by the wearing of plaster bandages for twenty weeks effected a reduction of the forward slipping from 12 to 3 mm. On the other hand, follow-up examinations revealed that in nine patients, two of whom had been treated by massage only, reduction of the subluxations occurred spontaneously (incomplete in six and complete in three).

Recumbency alone relieves the spasm considerably, but is more effective when combined with traction. However, straight traction in bed has proved totally ineffective in diminishing the forward displacement of the atlas unless the head is hyperextended.

Roentgenograms taken while heavy traction was being exerted on the head showed separation of the cervical vertebrae, but when the traction acts in the direction of flexion it has no influence in lessening the forward subluxation.

Jacobs,<sup>3</sup> who first reported cases of distention subluxation, noted while checking his manipulation by digital examination of the pharynx of one patient that the prominence of the subluxated lateral mass of the atlas disappeared when the head was hyperextended and promptly reappeared when the head was flexed. Berkheiser and Seidler<sup>7</sup> used traction with hyperextension in their five cases of distention subluxation and secured reduction in all of them.

Hyperextension is an important principle in the treatment of this condition. Not only do the movements of the vertebrae when hyperextended represent the reverse of the movement by which the subluxation took place, but recurrence of the deformity is prevented by the tension produced on the anterior spinal ligament, which then acts as a splint to the vertebrae. Light traction in hyperextension secured reduction within a week's time in two patients now under treatment and not included in this series.

Reduction accomplished, the head and neck should be rested for a sufficient time to allow for a subsidence of the inflammation and restoration of the transverse ligament to its normal length and strength. Subsidence of the inflammation can be judged clinically from the disappearance of muscle spasm, and roentgenographically from the disappearance of swelling of the soft tissue. The speed of restoration of the transverse ligament depends on the age of the patient, the length of time the subluxation has been present, the extent of the subluxation and the patient's general condition. Rest is most readily secured by immobilization in plaster in hyperextension. The period of immobilization might be varied, depending on the conditions mentioned, from three weeks to five months. Immobilization should never be maintained in flexion, and the position should be checked roentgenographically. A short period in bed to allow the muscles to regain their tone should follow removal of the support. A check-up by roentgen examination should be made shortly after the patient is allowed to be out of bed without support.

*Simple Rotation Deformity.*—In the eight cases in this group reduction with restoration of function was accomplished regardless of the form of treatment applied. Treatment employed included: massage only (two cases), wearing of a Thomas collar for two weeks, traction in bed for eighteen days, wearing of a plaster helmet for five weeks (two cases) and Walton manipulation with the helmet for five weeks.

One patient whose deformity resulted from overcorrection of a congenital torticollis following a myotomy was completely and permanently relieved by one day's traction in hyperextension.

7. Berkheiser, E. J., and Seidler, F.: Nontraumatic Dislocations of the Atlanto-Axial Joint, J. A. M. A. 96:517 (Feb. 14) 1931.

The same principles of treatment probably apply to this group as apply to distention subluxations, but, owing to the minor nature of the injuries sustained by the joint structures, immobilization following reduction is brief or may be omitted altogether.

*Fracture of the Atlas.*—Anatomic reduction of a fractured atlas is impossible by any method known at present. Relief from spasm of the muscles and the trauma of bearing weight by traction in bed is indicated for such a period as will allow union to take place, and protection from motion by a suitable collar after the bearing of weight is deemed safe.

#### PROGNOSIS

The length of follow-up in the series varied from three months to seven years, with an average of two years. Patients were regarded as well if they had no symptoms, no clinical deformity and a good range

TABLE 2.—*Results in Eighteen Cases of Distention Subluxation*

	Well	Improved	Unimproved
A. Age 5 to 10.....	5	3	0
10 to 15.....	3	1	1
15 to 20.....	0	2	1
Over 20.....	0	0	2
B. Original forward displacement			
5 mm. or under.....	6	3	0
Over 5 mm. ....	2	3	4
C. Reduced.....	3	0	0
Partly reduced.....	5	2	0
Unreduced.....	0	4	4

of motion in all directions without spasm; improved if there was any definite lessening of the original symptoms or any definite improvement in mobility; unimproved if there was negligible or no improvement in symptoms and physical signs.

The subluxations were classified as reduced, partially reduced and unreduced. The anterior atlantodental interval was measured in millimeters, and the subluxation was considered reduced if this distance was 2 mm. or less. All reductions with the exception of one partial reduction were spontaneous and were not secured under treatment.

Table 2 gives a summary of the results of treatment in eighteen cases of distention subluxation.

It may be concluded that the younger the patient is the smaller the amount of the original forward displacement, and the greater the amount of reduction secured the better are the results. In only one case was there any increase in the subluxation six months after it was recognized. It is assumed that after the acute inflammation has subsided there is little tendency to further stretching of the transverse ligament.

All the patients with simple rotation deformity made a complete recovery.

The two patients with fractured atlantal arch recovered a good range of motion, but both continued to suffer from pain in the neck, particularly in damp weather and on resuming activity after resting.

#### SUMMARY

Nonfatal dislocations of the atlas without fracture of the dens must be rare. Subluxation of the atlas forward is not uncommon and is associated with relaxation of the transverse ligament. Subluxation is often accompanied by rotation deformity, but rotation deformity often exists without subluxation. Roentgenographically, subluxation is diagnosed by the increased anterior atlantodental interval; rotation deformity, by the deviation of the spine of the epistropheus. Effusion in the atlanto-epistropheal joints, resulting from rheumatic fever or from foci of infection nearby, causes the relaxation of the transverse ligament and the subluxation. Simple rotation deformity is usually caused by minor trauma. Pain, stiffness, deformity, limitation of motion in the neck and spasm are found in both subluxations and rotation deformities. Bilateral subluxation is characterized by flexion of the head and a prominent epistropheal spine in the midline. Unilateral subluxation and rotation deformity are characterized by flexion, rotation, tilt and deviation of the epistropheal spine to the side toward which the head is turned. Traction in hyperextension will reduce both subluxations and rotation deformities. Immobilization should last long enough to allow recovery of the damaged structures of the joints, especially the transverse ligament. Subluxations show little tendency to increase six months after the original slipping; rather they tend to decrease spontaneously. The younger the patient and the less marked the subluxation, the better the prognosis.

#### CONCLUSION

Patients with an acquired torticollis, especially when giving a history of rheumatic fever or infection about the head and neck, should be studied roentgenographically. If an atlanto-epistropheal subluxation or rotation deformity is found, traction with hyperextension followed by immobilization in hyperextension is the treatment of choice.



# LOCAL ATROPHY OF BONE

## III. EFFECTS OF VITAMIN D AND OF CALCIUM ON LOCAL ATROPHY AND UNION

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DETROIT

AND

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Convalescence after fractures of and operations on bone is prolonged because bone heals more slowly than does soft tissue and because the immobilization required during the process of healing leads to local atrophy of the bone and muscles and to a decrease in the range of motion permitted by the soft tissues of the part. If the union of bone could be hastened and if local atrophy could be prevented considerable economic advantage would result and a proportionately larger number of patients could be treated in orthopedic hospitals each year with the same number of beds. In this article we report a series of clinical experiments in which therapeutic doses of vitamin D and of calcium were administered to normal children receiving an adequate diet in an attempt to hasten union and to prevent local atrophy of bone after stabilizing operations on the feet.

We know of no observations on the effects of added vitamins and calcium on local atrophy of bone in animals receiving an adequate diet, but a considerable literature has accumulated on the effect of these substances on the union of bone. There is general agreement that if animals are given a scorbutic diet the union of fractured bones will be delayed or will fail to occur, depending on the severity of the avitaminosis.<sup>1</sup> However, an excess of vitamin C administered to an animal receiving a normal diet has no effect on the healing of fractures (Israel and Frankel,<sup>2</sup> Schilowzew,<sup>3</sup> Roegholt<sup>4</sup> and Holasz and Marx<sup>5</sup>).

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1. Watanabe, T.: Experimental Researches on Effect of Avitaminosis on the Healing of Bone Fractures, *Virchows Arch. f. path. Anat.* **251**:281, 1924.

2. Israel, A., and Frankel, R.: The Influence of Vitaminosis on the Healing of Fractures, *Klin. Wchnschr.* **5**:94, 1926.

3. Schilowzew, S. P.: The Influence of Avitaminosis, *Deutsche Ztschr. f. Chir.* **209**:320, 1928.

4. Roegholt, M. M.: The Influence of A, B, C and D Vitamin and the Elements of Calcium and Phosphorus on the Healing of Fractures, *Arch. f. klin. Chir.* **168**:783, 1931.

5. Holasz, G. V., and Marx, Josef: Is Callus Building Influenced Through the Addition of Vitamin C? *Arch. f. klin. Chir.* **169**:121, 1931.

Observers who have added vitamin D and calcium to an adequate diet have reported conflicting results. Bors<sup>6</sup> and Collazo<sup>7</sup> found that the addition of vitamin D to the diet increased the size of the callus and the rapidity of the union of fractures in rats as compared with control rats which were given an adequate diet. Roegholt<sup>4</sup> found that an insufficient amount of vitamin D caused delayed union, but made no observations on the effect of an excess of vitamin D in the diet. Moritsch and Krammer<sup>8</sup> and Pincussen and Newmann<sup>9</sup> administered a substance which contains vitamins A, B, C and D, calcium and phosphorus to experimental animals and to patients with fractures, and concluded that this substance caused fractures to unite more rapidly than did similar fractures in animals and patients receiving a normal diet. On the other hand, Hellner,<sup>10</sup> Vara-Lopez,<sup>11</sup> Swart<sup>12</sup> and Lewis<sup>13</sup> found that the addition of an excess of vitamin D to an adequate diet had no effect on the healing of fractures, and Tammann<sup>14</sup> found that the addition of a large excess of vitamin D to the diet of rabbits with experimental fractures had a deleterious effect on the callus and in some instances caused atrophy or fracture of the callus.

After we had found that atrophy of bone could be demonstrated in roentgenograms of a foot which had been immobilized in a plaster of paris cast and had gained a fair idea as to the amount of atrophy which might be expected to occur after eight weeks of immobilization, we decided to use postoperative roentgenograms of the feet as criteria in determining whether or not the atrophy could be prevented by adding vitamins and calcium to the diet.

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6. Bors, E.: Vigantol and Fracture Healing, *Zentralbl. f. Chir.* **54**:3266, 1927.

7. Collazo, J. A.; Rubina, P., and Varela, B.: The Rôle of Vitamin D in the Regeneration of Bone Tissue and Callus Building in Experimental Fractures, *Arch. f. klin. Chir.* **158**:214, 1930.

8. Moritsch, P., and Krammer, E.: The Influence of a Calcium and Phosphorus Containing Vitamin Preparation (Vito Phos) on Callus Building, *Wien. med. Wchnschr.* **79**:1454, 1929.

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12. Swart, H. A.: The Effect of Irradiated Ergosterol on the Healing of Experimentally Produced Fractures in Animals, *J. Bone & Joint Surg.* **12**:360, 1930.

13. Lewis, K. M.: Non-Effect of Irradiated Ergosterol in the Treatment of Fractures, *Ann. Surg.* **92**:415, 1930.

14. Tammann, H.: Retardation of Fracture Healing by Vitasterin, *Arch. f. klin. Chir.* **165**:475, 1930.

For the purpose of our studies we selected children in good general health who were to be subjected to stabilization operations on one or both feet. In most instances the operation was the classic Hoke operation consisting of a subastragaloid arthrodesis and a plastic osteotomy of the neck of the astragalus with an arthrodesis of the astragaloscaphoid joint. In some instances the calcaneocuboid joint was subjected to arthrodesis (triple arthrodesis). Thus we had a series of patients with a fairly uniform surgical procedure in whom we could

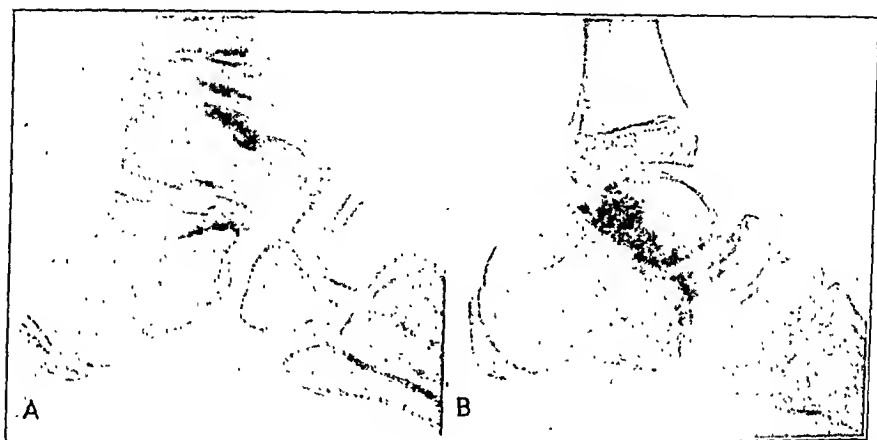


Fig. 1 (B. Z.).—The left foot: *A*, before the operation, and *B*, eight weeks after a Hoke operation and immobilization in a plaster of paris cast. This patient received cod liver oil twice a day during the period of immobilization.

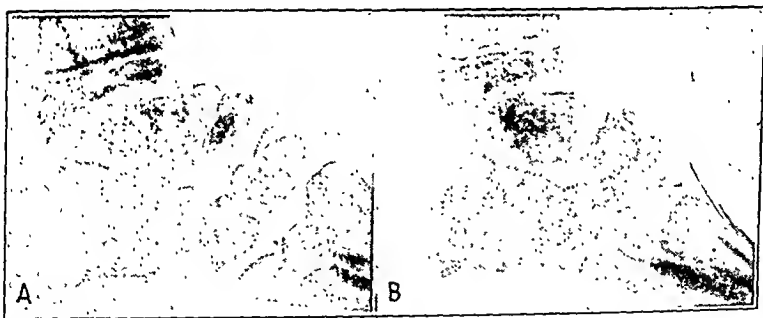


Fig. 2 (A. W.).—The left foot: *A*, before immobilization, and *B*, after operation and immobilization for ten weeks in a plaster of paris cast. This patient received cod liver oil and calcium during the period of immobilization.

study the degree of atrophy and the rapidity of union between the bones at the healing joints. After the operation it is customary to keep the foot and leg immobilized in a plaster cast which extends from the middle of the thigh to the toes. The immobilization is continued for eight weeks. Then the cast is removed and the patient begins to walk in an ordinary shoe.

Forty patients were studied. Ten of these were used as controls and received the ordinary hospital diet at the Shriners' Hospital for

Crippled Children, which is an adequate diet for normal children. The other thirty patients received the same diet, but in addition, ten received viosterol (20 drops daily), seven received cod liver oil<sup>15</sup> (2 teaspoonfuls daily) and the remaining thirteen received cod liver oil and calcium (2 teaspoonfuls of cod liver oil and 2 teaspoonfuls of calcium compounds—about 1 Gm. of calcium phosphate daily).

At periods of from seven to eight weeks after the operations the casts were removed, lateral roentgenograms were made of the feet, and the feet were examined clinically. Other than some separation of the edges of the skin, which is a frequent occurrence after these operations, there were no complications in the series, and complete healing had taken place at the end of the usual eight weeks' period. No difference in the healing was noted when the controls were compared with the patients who received the added vitamin D and calcium. The same was true of the stability of the feet. On clinical examination and functional tests the feet of the controls appeared to be as stable and as firmly united as the feet of those who had received the added vitamin D and calcium.

When the roentgenograms of the feet were studied and compared with preoperative roentgenograms of the same feet, and when those of the controls were compared with those of the patients who had received the added vitamin D and calcium, it was found that there was about the same degree of atrophy of bone and of roentgenologic evidence of union of bone in both series.

#### COMMENT

The observations recorded in this article indicate that local atrophy of bone is the result of local conditions and that it cannot be prevented or appreciably lessened by an abundance of vitamin D and calcium in the diet. Likewise, the healing and union of bones appear to require a certain amount of time, and we found no evidence that the addition of vitamin D and calcium to an adequate diet will reduce this time.

It is to be emphasized that all our patients received an adequate diet and our results are not to be interpreted as evidence that patients convalescing from fractures and operations on the bones should not receive vitamin D and calcium. It is probable that a diet deficient in vitamin D and calcium would lead to increased local atrophy and delayed union of bone.

It is further to be noted that therapeutic doses of vitamin D and calcium do not cause increased local atrophy or delayed union of bones.

#### CONCLUSION

The addition of vitamin D and calcium to an adequate diet does not lessen local atrophy of disuse or accelerate the rate of union of bones.

<sup>15</sup> The cod liver oil contained 20,000 vitamin A and 10,000 vitamin D units to the ounce (29.5 cm.).

# A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 170)

## PROSTATE GLAND

*Carcinoma.*—Young<sup>27</sup> stated that carcinoma of the prostate gland generally begins as a nodule just beneath the posterior capsule, where it is easily palpable by way of the rectum. Hypertrophy of the prostate gland almost never begins in this region, and the two may develop concurrently, each occupying a different part of the gland; in fact, 50 per cent of patients with carcinoma of the prostate gland also have adenomatous hypertrophy, not infrequently quite remote from and entirely uninvolved by the carcinoma. Later the carcinoma spreads in all directions, ultimately penetrating the fibrotic capsule of the adenomatous enlargements and finally completely replacing the nonmalignant cells within such capsules.

Young described his radical operation for the care of the prostate gland: After exposing the gland through an inverted V incision by the usual division of the central tendon and recto-urethral muscle, it is opened through the membranous urethra, a retractor is introduced and the posterior surface of the gland is exposed. The radical operation is begun by transverse division of the urethra, isolation of the prostate gland from beneath the anterior transverse fascia, exposure of the bladder near the prostate gland and resection of the cuff of the bladder

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27. Young, H. H.: The Ultimate Results in the Treatment of Carcinoma of the Prostate by the Radical Removal of the Prostate, Vesical Neck and Seminal Vesicles, *J. Urol.* 29:531. (May) 1933.

with transverse division of the trigon about 1 cm. below the urethral orifice. The bladder is then pushed up, care being taken not to injure the ureters, and the ampullae and vesicles are isolated, clamped, divided and ligated high up. Careful hemostasis must be obtained. The new high frequency coagulation machine is of great assistance, but the deep pedicle of the seminal vesicles should be ligated and all serious bleeding stopped. No difficulty is experienced in anastomosing the bladder to the membranous urethra, a portion of the anterior wall being used and the remainder closed longitudinally. A retained urethral catheter takes care of drainage. The deep angles of the wound are lightly packed with a long strip of iodoform gauze, which is brought out through one corner of the wound, the rest of the wound being closed by interrupted sutures of waxed silk.

Young stated that this operation, which at first seemed so formidable, has been carried out in 42 cases at this clinic; it has also been carried out in 40 cases by G. G. Smith at the Massachusetts General Hospital, who stated that one and a half hours suffice for the operation, that the mortality rate is no greater than in prostatectomy for benign hypertrophy, and that healing is accompanied by less infection and is often quicker. Young's statistics indicate that of 4,295 operative prostatic specimens, 460, or 10.7 per cent, revealed carcinoma. If cases were included in which treatment was with radium, the percentage of carcinoma would be higher. These statistics demonstrate the great importance of recognizing carcinoma and recognizing it early.

The average age of Young's 42 patients, for whom the radical operation for carcinoma of the prostate gland was employed, was 64 years; the youngest patient was 51 years of age and the oldest, 77. The predominant symptoms were: frequency, nocturnal emission, complete retention, urethral discharge, burning on urination, hesitancy, hematuria, urgency and difficulty in completely emptying the bladder; several patients made no complaint. The anesthetic agent employed was ether in 9 cases, and oxygen and ether in 15. Anesthesia was caudal in 15 cases, and spinal in 3. The average number of days in the hospital was forty-two. The mortality rate was 4 deaths, or 9.5 per cent; in the last 37 cases the rate was 2 deaths, or 5.4 per cent. Twenty-seven patients have been traced who left the hospital after the radical operation, now more than five years ago. Of these, 11 of the original 42 patients, or 26 per cent, have lived five years without recurrence. Fourteen patients are living, only 3 with recurrence, at periods varying from one to seventeen years after operation. Ten of these patients control perfect urinary control.

Young stated that the principal object of his explanation of the results was to demonstrate, first of all, that early diagnosis of carcinoma of the prostate gland is generally easy. A very hard nodule, palpable

by rectum, unless shown to be a stone by a roentgenogram, should be looked on with grave suspicion. In such a case the patient should be subjected to perineal operation at which the lesion can be seen, palpated and, if necessary, incised and studied microscopically. If physicians could be taught to make rectal examinations much more frequently and to be suspicious of every markedly indurated prostate gland, even when only a small nodule is present, many patients would be brought to early radical operation and to ultimate cure. Young stated that freedom from recurrence can be obtained in a large percentage of cases, and that excellent functional results with complete nocturnal control can be secured in practically every case; he also stated that diurnal control can be obtained in a large percentage of the cases when the patient is on his feet.

Smith<sup>28</sup> stated that in early prostatic carcinoma, before the growth has extended beyond the capsule of the gland, the possibility of cure is encouraging, but there are few cases in which the condition is discovered while patients are in this stage. When the growth has developed beyond this point, the question of cure is no longer pertinent; the object of treatment then is to relieve urinary obstruction, if that exists, and to retard, as much as possible, further growth. Smith reviewed 25 cases of carcinoma of the prostate gland in which high voltage roentgen treatment was given. Eighteen of the patients suffered from pain in the back, legs or pelvis; all of them were relieved following irradiation. This relief varied in degree from partial to complete, and in duration from one to six months. One series of treatments frequently relieved pain for three months. The prompt relief from pain was sometimes remarkable. The effect of irradiation on the prostate gland itself was less pronounced. In 9 cases the gland appeared to be smaller after treatment; in 10 it continued to increase in size, and in 2 it gave no evidence of change. The degree of urinary obstruction was not affected.

Smith reviewed the results of treatment with radium in 29 cases of carcinoma of the prostate gland. In 3 cases treatment consisted in insertion of seeds or needles through the perineum; in 11 cases partial perineal prostatectomy was performed with implantation of radium in the remaining shell of prostatic tissue, and in 16 cases radium was implanted through the open bladder. In most of these cases the obstructing median bar was removed at the same time; in 2 others, radium was implanted in the tips of vesicles after total perineal prostatectomy. Smith reported that in 29 operations, there were 6 operative deaths, or 21 per cent. Three were due to embolus, 2 to cardiac failure and

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28. Smith, G. G.: *The Treatment of Cancer of the Prostate*, New England J. Med. 208:57-(Jan. 12) 1933.

1 to sepsis. Sixteen patients died of carcinoma, the average length of life after operation being thirteen months. Of 6 patients known to be alive, 1 has lived four years. He is incontinent and has sclerosis of the vesical neck and a bladder that holds only 1 ounce (30 cc.). He is losing weight, and although roentgenograms do not show bony metastasis, he looks cachectic. Three other patients are having considerable trouble, and 3 patients, who were operated on recently, although they have good control, have strangury and pain at the neck of the bladder.

Smith felt that of all surgical methods of attacking carcinoma of the prostate gland, total perineal prostatectomy is the only really aggressive one. He also reviewed his surgical cases for evidence of malignant disease of the prostate gland; he has operated on 42 patients in the last thirteen years. In all cases, the diagnosis has been established by microscopic examination. There were 3 operative deaths. Seventeen patients died of carcinoma, with an average duration of life of twenty-seven months. Four patients are alive but give evidence of local recurrence or metastasis in the spinal column. None of these has any urinary obstruction. Seventeen patients are alive and apparently well. Of 13 who are alive and free from recurrence or metastasis, 6 have lived five or more years since operation; of the 11 who died without recurrence or metastasis, 5 lived five or more years. Smith concluded by saying it is his conviction that in early cases of prostatic carcinoma total prostatectomy should be done.

Smith, in a second article,<sup>29</sup> stated that perineal prostatectomy for carcinoma is not a particularly difficult operation to perform. He has found that the time required to perform this operation is about an hour and a half. It can generally be done with one application of spinal anesthesia, particularly if nupercaine is used. He stated that convalescence has been unusually easy; in fact, it is less fraught with anxiety than after ordinary prostatectomy because there seldom is any bleeding, and there seems to be no toxic absorption, or at best very little, from the space from which the prostate gland is removed. Since 1918, Smith has performed 41 of these operations. Of the patients operated on, 4 died in the hospital, and 13 who survived the operation died of carcinoma of the prostate gland. The average length of time between operation and death was twenty-one months; the longest, seven and a half years. In 2 cases, in both of which death finally resulted from carcinoma originating in the prostate gland, the patients, as far as they knew, had been well between five and six years after operation; local recurrence then developed with metastasis, and the end came fairly rapidly.

<sup>29</sup> *Ann. Surg.*, 1924, 78, 1, 100; also *Ann. Surg.*, 1925, 80, 1, 571.



An important point is that in these cases there are no local symptoms in regard to difficulty of urination after operation.

Smith reported that several of the papillary tumors which he encountered were of the type in which the neck of the bladder is involved and the tumor is malignant, as had been proved by biopsy and cystoscopic inspection. With improvement of the modalities of high frequency current, Smith found that by using a flexible-loop electrode he could ream out the whole neck of the bladder and the tumor without any difficulty, whereas in all these cases operation previously had been by the suprapubic route. In another type of case, which has presented difficulties in the past and necessitated laborious, frequent treatment for large papillomas, Smith, with the same type of electrode, has been able to cut down the tumors (tumors of enormous size) so that within two or three treatments the whole tumor has been destroyed, the superabundant mass being cut away with the loop electrode and the base immediately coagulated with the ordinary button electrode.

*Transurethral Resection.*—Bumpus<sup>30</sup> stated that in the sixteen months from Jan. 1, 1932, to July 1, 1933, at the Mayo Clinic, 488 patients were subjected to transurethral resection of the obstructing portion of the prostate gland. Only 1 patient of this group died. In a recent study, 600 cases in which prostatectomy was performed were compared with 600 cases in which resection was done; 43 per cent of the patients who were subjected to prostatectomy had been prepared by permanent drainage with a catheter, whereas only 24 per cent of the other group were so prepared. Of these 1,200 cases, suprapubic cystostomy was performed in 45 per cent of the cases in which the patients were to undergo prostatectomy and in 19 per cent in which the patients were to undergo transurethral resection.

Bumpus reported that when transurethral resection for prostatic obstruction was first undertaken, only those cases were included in which obstruction was minimal. The field has gradually enlarged, however, until, in the first six months of 1933, only 3 patients underwent suprapubic enucleation of the gland, whereas 202 patients underwent transurethral resection. Bumpus felt, therefore, that, with few exceptions, prostatic obstruction can be corrected by transurethral methods if the urethra permits the passage of instruments. He stated that transurethral resection has been criticized as a more or less temporary measure. He reported that from Jan. 1, 1925, to Jan. 1, 1932, he had removed tissue which, on microscopic examination, revealed adenofibromatous hypertrophy in 96 cases. In 1 case in which operation had been performed in 1925, 8 Gm. of tissue was removed, a considerable amount for those

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30. Bumpus, H. C., Jr.: Preparation for, and Care Following, Transurethral Resection of the Prostate Gland, *Urol. & Cutan. Rev.* **37**:674 (Oct.) 1933.

days. When last traced, 86 of these patients were alive and 68 were satisfied with the results of operation, many after a lapse of more than four years. From January 1927 to July 1933, subsequent prostatectomy was required in only 9 (1.3 per cent) of 702 cases in which transurethral resection had been performed. During the same period, transurethral resection has been employed in 21 cases in which prostatectomy had been performed previously.

Walker<sup>31</sup> discussed the anatomy and physiology of the vesical neck and pointed out that resection is rendered more difficult by the fact that the knowledge of its anatomy and physiology is so incomplete. An examination of the muscle fibers of the vesical neck would indicate, in Walker's opinion, that opening of the neck of the bladder is brought about not merely by relaxation of the sphincter but also by the dilating action of certain longitudinal fibers passing through this structure. In discussing pathologic changes in the vesical neck, Walker made use of the term "dysectasia," previously introduced by Legueu, to indicate the condition in which there exists some obstacle to the opening of the neck. He then discussed the histology of obstruction of the vesical neck under the following divisions: (1) glandular hyperplasia, (2) muscular hypertrophy, (3) increase of fibrous tissue, (4) increase of more than one tissue and (5) malignant disease. After stating that the aim of operation is to remove all tissue that interferes with normal opening of the neck, Walker considered the various routes by which the neck may be approached, namely, the perineal, the suprapubic and the transurethral. The operation of cuneiform excision of the posterior lip of the internal meatus was then described as well as the more radical operation of complete excision. He then described transurethral methods, starting with the history of transurethral operations and ending with a description of instruments in present use. He pointed out that modern transurethral methods are of three kinds: simple fulguration, the coagulated tissue being left to slough away subsequently; electrocoagulation followed by immediate punching out of coagulated tissue; removal of obstructing tissue by means of the McCarthy loop. Walker said that in his experience sepsis is a grave danger in all cases in which coagulated tissue is left behind, and for that reason he expressed a strong preference for operations that include immediate removal of coagulated tissues. In his opinion, this removal may best be accomplished by the use of the McCarthy loop which removes tissue at the same time as it seals off bleeding points.

Walker stated that since the aim of surgical intervention is to remove enough tissue to restore the ability of the neck to dilate, transurethral

31. Walker, Kenneth: The Surgery of the Bladder Neck. Fifth Cong. Internat. Soc. Urol., 1933, p. 516.

operation must be employed only when, in the opinion of the operator, this aim can satisfactorily be achieved by such methods. When surrounding structures are extensively involved, as, for example, in a case of fibrous "bar" associated with a fibrous prostate gland, the more radical operation of excision of the neck will probably be required.

Scholl<sup>32</sup> stated that transurethral prostatic resection is unquestionably a procedure that will be used extensively in the future. The recognition of early obstruction and treatment by resection while the patient is still in good health will greatly reduce the incidence of advanced prostatism and its need for extreme surgical procedure. He stated that prostatic resection is definitely not a minor operation. It carries a high potential risk, even in the hands of an expert, and it should be done only after thorough examination and adequate preparation by a urologist specially skilled in the technic. The ready acceptance of this procedure by physicians for their own personal needs suggested to him a successful future for the method.

Weijtlandt<sup>33</sup> stated that disturbances in evacuation of the bladder due to lesions of its neck may be classed under the clinical name "prostatism." In the great majority of cases such disturbances are caused by adenoma of the submucous periurethral glands (prostatic hypertrophy) or by carcinoma of these glands or of the prostate gland (prostatic carcinoma) or by sclerotic processes fundamentally of an inflammatory nature. The cause of urinary retention in such cases is not, as a rule, the purely mechanical "cut-off" of the urinary passage; a catheter, for instance, can usually be passed. The most common cause of retention is some obstacle to the functioning of the sphincter in the process of opening. This is due partly to mechanical fixation of the muscle by pathologic tissue and partly to secondary hypertony of the sphincter.

Weijtlandt reported that the various operative measures applied, such as prostatectomy, extirpation of the vesical neck, cuneiform excision, punch operation, electrocoagulation and "cutting current" resections, are all the same on one point, namely, removal of a portion of the pathologic tissue from the region of the vesical neck and sphincter. The success of this procedure depends on whether sufficient tissue is removed to allow what remains of the vesical neck and of the prostatic urethra to regain a sufficient degree of flexibility, or, at all events, to prevent the sphincter from being impeded in its function of opening the vesical neck. There are three methods of transurethral treatment which are well known: Young's punch operation, or one of the modified forms of the Braasch-

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32. Scholl, A. J.: *An Evaluation of Transurethral Prostatic Resection*, West. J. Surg. **41**:278 (May) 1933.

33. Weijtlandt, J. A.: *On the Surgery of the Bladder Neck*, Fifth Cong. Internat. Soc. Urol., 1933, p. 477.

Bumpus, McCarthy or Day and Phélip operations; Caulk's cautery-punch operation, and the "cutting-current" resection methods of Stern-Davis, McCarthy, Canny Ryall and of von Lichtenberg. Weijlandt concluded that the results thus far reported do not warrant any definite conclusions. Publication of more detailed reports on more cases will be required to make it possible to form a solid judgment regarding these therapeutic methods, the indications for and the practical performance of them, the attendant danger and their efficacy over long periods of time.

*Electrosurgical Resection.*—Belt, Charnock, Folkenberg and Falconer<sup>34</sup> described a current activator for prostatic resection which is amply powered, compact and inexpensive. It has an undamped current which is supplied by vacuum tubes and which is suitable for cutting under water. A spark-gap apparatus furnishes a damped current for the coagulation of bleeding vessels.

A series of experiments were carried out which indicated that the optimal density of the radio frequency current for adequate under-water cutting was 300 volts and 0.7 amperes. It was discovered that the death of cells occurred for an appreciable distance beyond the actual cut if the density of the current was increased to 325 volts and 1.8 amperes. Healing subsequent to cuts made with such a current proceeded along the cut edge without the death of an appreciable amount of tissue beyond the point of contact with the advancing loop. These investigators further discovered that a coagulating current of low wattage, when held in contact with the surface of the prostatic urethra for a length of time sufficient to whiten the tissues, caused death of cells to great depths. The depth of the subsequent slough bears a direct relation to the length of time the active electrode is in contact with the tissues.

*Disease of the Vesical Neck.*—Marion<sup>35</sup> stated that from a symptomatic point of view it is evident that there are two types of disease of the vesical neck. In the first, or so-called congenital type, the manifestations appear in early childhood; in the second type, the trouble arises at a later age, without ever having been preceded by other disturbances. In the congenital form, complications occur early in infancy. The child is obliged to use pressure when urinating. He takes a long time to urinate, and this is sometimes noticed by the parents. The symptoms then increase more or less rapidly. They are comparable in every way with the manifestations of prostatic hypertrophy and vary slightly according to the patient; there is, sometimes, incomplete retention with-

34. Belt, Elmer; Charnock, D. A.; Folkenberg, A. W., and Falconer, R. A.: The Current Activator in Electro-Surgical Resection of the Prostate, *Urol. & Cutan. Rev.* 37:687 (Oct.) 1933.

35. Marion, G.: Maladie du col vésical, Fifth Cong. Internat. Soc. Urol., 1933, p. 451.

out distention, distinguished by more or less pronounced pollakiuria and the presence of residual urine in more or less abundant quantities. This incomplete retention occasionally leads to distention with incontinence. Finally, and frequently, the dysuric stage is abruptly intensified by complete retention.

The acquired type of disease of the vesical neck has symptoms identical with those of the congenital type, which in turn are identical with those of prostatic hypertrophy; in these cases, however, it has been impossible to trace dysuric trouble in infancy. The symptoms appear at a more or less advanced age and develop rapidly. In such cases there invariably are urethral or periurethral antecedents, such as long-standing chronic urethritis, often accompanied by periurethral suppuration and stricture.

#### BLADDER

*Tumors.*—Sindoni,<sup>36</sup> in a case of primary adenocarcinoma of the bladder, studied the vesical mucosa with reference to the existence of vesical glands, a subject about which there is no unanimity of opinion today. Albarran gave the most detailed description of these glands, which he divided into two groups: The first group of glands are near the trigon and consist of small depressions, which do not have a membrana propria, only a simple wall of connective tissue lined with an epithelium not essentially different from that of the epithelial cells of the bladder. These glands do not secrete mucus but contain cellular detritus due to superficial epithelial desquamation. The second group is situated outside of the neck of the bladder, especially on the anterior wall, and the glands are analogous to those of the first group, and still rudimentary. Contrary to Albarran's opinion and that of investigators who agreed with him, there are a number of other investigators who think these formations are not glands but only glandlike depressions.

In view of such differences of opinion, Sindoni took up the histologic study of these structures for himself in healthy bladders, examining only the trigon. He found that whereas the gross appearance of these structures was somewhat varied, the histologic details were uniform: at times there were superficial excavations of the epithelium, and in other cases simple or ramified tubular formations, but the epithelium in all was exactly the same as that of the surface and the connective tissue had the same structure. In fact, the tunica propria followed the outlines of the glandlike formations and was composed of fibrillar connective tissue and elastic fibers. Sindoni concluded that both in children and in adults there are solid epithelial masses and simple or branching tubular formations at the vesical trigon which in their structure must be regarded

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36. Sindoni, M.: Glandule vesicali e tumori a struttura glandulare della vescica, Arch. ital. di urol. 10:309 (July) 1933.

as minute extroflexions of the mucosa. Despite the fact that the gross appearance of these structures is that of glands, he thinks such a name cannot be given to them, because the term "gland" is closely bound up with the idea of secretion, and there was no histologically observable secretion. A mucicarmin test gave negative results. Sindoni denied the existence in the bladder of any true mucous glands, and he thought that to explain the genesis of local glandular neoplasms "of cylindric epithelium" the view must be taken that these are in some cases tumors starting in the prostate gland and in others heterotopic epithelial inclusions, or else that they are a process of metaplasia of the vesical epithelium.

[COMPILER'S NOTE.—The subcervical group of glands of the vesical neck and region of the trigon have been recognized as a clinicopathologic entity since Albarran's time and, as is evident from the literature, their existence as true glandular formations has been confirmed by many investigators. Lowsley, in a study of a series of postmortem examinations, discovered that they were present in 32 per cent of the cases. Likewise, these subcervical glands or tubules have been recognized as an entity, since they tend to cause adenomatous hypertrophy, infection and other pathologic conditions which produce obstruction at the outlet of the vesical neck. The subcervical glands of Albarran may likewise undergo adenocarcinomatous hypertrophy independent of the prostate gland itself, and they may thus give rise to a pedunculated tumor of the bladder. Folsom described them in relation to the urethra and vesical neck of the female and, more recently, Gutierrez, in a review of the literature, explained how they may produce pathologic conditions affecting the vesical neck.]

*Carcinoma.*—Watson<sup>37</sup> reported 411 cases of carcinoma of the lower portion of the urinary tract in which treatment was given at the New York Institute. In this study there were 204 cases of carcinoma of the bladder, 194 cases of carcinoma of the prostate gland, 11 cases of carcinoma of the urethra and 2 cases of carcinoma of a fistulous tract leading from the bladder. The cases of carcinoma of the bladder were divided into: (1) Carcinoma of the bladder, papillary or undifferentiated in type. In this group there were 32 cases; 5 patients were lost from observation after having been treated on an average of seven months after coming to the hospital, and 3 were not treated. Twenty-four patients were treated, and of these 3 were alive and gave no evidence of tumor a year and six months, two years and four months and ten years and one month, respectively, after starting treatment. Of the 21 patients who died, the duration of life after starting treatment had been an average of eight months. (2) Adenocarcinoma, an uncommon type of

<sup>37</sup> Watson, E. M.: A Study of Carcinoma of the Lower Urinary Tract, *J. Urol.* 29:545 (May) 1933.

vesical tumor arising from aberrant prostatic tubules, from the subtrigonal group of glands or from mucous glands occasionally contained within the wall of the bladder. This type of tumor was encountered twice; in both cases the patients were men, aged 50 and 54 years, respectively. (3) Epithelioma of the mucous membrane. Histologically, these tumors, although deeply infiltrating and rather rapidly growing, retain to a pronounced degree the characteristics of cells of the mucous membrane lining the bladder. In this group there were 134 cases. In 4 of these treatment was not given for various reasons. Of the remaining 130 patients, 90 are now dead, and of those who are living, 25 have no vesical tumor and 14 still have varying amounts. One patient was lost from observation at the end of a year and three months, but at the time gave no evidence of tumor. (4) Malignant papilloma, designated as such because of the papillary arrangement of cells. These tumors possess, however, all of the malignant properties of the previously mentioned types, but to a less degree. There were 24 patients with tumors of this type. Three of these patients were lost track of after having been under observation for from eight months to seven years with no tumor present at the last examination. Fourteen have died, 12 of malignant tumor. Seven of this group are still living; 6 of these have no tumor, and 1 has tumorous tissue present. Of the patients who died, the duration of life, on an average, was two years and one month after starting treatment. (5) Massive papillomatous tumors, the cells of which arouse suspicion but lack the earmarks of malignancy possessed by tumors of the other groups. There were 13 cases in this group, and in 4 of these the patients had been lost from observation with no evidence of tumor when they last were seen. One patient has died after one year and five months, and 8 are alive without evidence of tumor from one to seven years after treatment.

Watson stated that 194 patients with carcinoma of the prostate gland were treated; 65 of these had undergone previous operations for the removal of the gland, 4 by the perineal route and 61 by the suprapubic route, at a time varying from one to six years before entering the hospital. Of the 194 patients, 111, or 57 per cent, had carcinomatous infiltration of both seminal vesicles in addition to prostatic growth when they were admitted, whereas 30, or 15 per cent, had only one seminal vesicle infiltrated in addition to the prostatic growth. Twenty are now living, on an average of eleven months after beginning treatment; 1 of these has lived ten years and four months, and another died after eight years and one month. In this group no proved cure has been obtained.

Smith and Mintz<sup>38</sup> studied and reported 150 cases of tumor in the bladder. In this group, 117 operations had been performed, excluding

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38. Smith, G. G., and Mintz, E. R.: Bladder Tumor, *Am. J. Surg.* 20:54 (April) 1933.

simple cystostomies; 35 patients, or 30 per cent, died following operation. Smith and Mintz concluded that the grade of malignancy of the tumor of the bladder has no demonstrable relation to its tendency to metastasize. Squamous cell carcinoma metastasized almost twice as frequently as papillary carcinoma. They stated that one important cause of the poor results from surgical treatment of carcinoma of the bladder is the long delay between the occurrence of the first symptoms and the patient's entrance to the hospital.

Smith and Mintz stated that a comparison of the results of resection, electrocoagulation and radium implantation gives evidence that the lowest number of deaths in the hospital is among patients treated by electrocoagulation (26 per cent); resection revealed the next lowest number, 32 per cent, and radium implantation revealed the highest, 41 per cent. The end-results from these three methods were approximately the same. Smith and Mintz expressed the belief that no one method is suitable for all types of carcinoma. The surgeon should be prepared to employ whichever method seems best in the individual case.

*Diverticulum.*—Kutzmann<sup>39</sup> stated that diverticulum of the urinary bladder is a disease that affects chiefly the male, and nearly always it is associated with such an obstructive condition as prostatism or urethral stricture. The incidence of diverticulum is as follows: in urologic cases in general, 1.2 per cent; in cases of benign hypertrophy, 9.1 per cent; in cases of contracture and median bar obstruction, 16.8 per cent, and in cases of urethral stricture necessitating operation, 14.3 per cent. No definite clinical symptoms are noted, except, possibly, that if there is obstruction of the lower portion of the urinary tract with infection, an accentuation of the characteristic symptoms of the associated condition is present. Kutzmann stated that diverticulum of the urinary bladder is the result both of congenital and of acquired anatomic factors. He also stated that this condition can be treated most satisfactorily by correcting the obstructing factors, diverticula being treated individually only when they are of the retention type or of large size. This method of procedure will give gratifying relief from symptoms which have been intense and of long duration.

*Cystostomy.*—Goldstein<sup>40</sup> stated that emergency or early suprapubic cystostomy should always be performed when the catheter is giving unsatisfactory urinary drainage, when the urethra or bladder is ruptured, when the condition of the patient seems to be aggravated by the

39. Kutzmann, A. A.: Diverticulum of the Urinary Bladder: Analysis of 100 Cases, Surg., Gynec. & Obst. 56:898 (May) 1933.

40. Goldstein, A. E.: Emergency Suprapubic Cystostomy, J. Urol. 29:609 (May) 1933.



presence of a urethral catheter and when patients with urinary obstruction have sensitive urethras.

Beer<sup>41</sup> enumerated the underlying causes of persistent and recurring suprapubic fistula following cystostomy. In the local group, the outstanding causes are improper surgical technic and partial prolapse of the vesical wall between the rectus muscles, gauze sponges left in the bladder, contracted bladder, overlooked large, infected diverticula and disharmony between the sphincter and the detrusor muscles. In the peripheral group, the causes of fistula are unrelieved obstruction at the neck of the bladder, fibrous vesical neck, adenoma and stones or stricture in the urethra. In the third group, central, Beer stated that infected kidneys, infected hydronephrosis and tuberculous kidneys are the main causes.

*Injury.*—Stevens<sup>42</sup> summarized the histories of 8 women whose bladders had accidentally been torn or incised during the course of a pelvic operation. In 2 cases, injury to the bladder had occurred during hysterectomy; in 2 cases during hysterectomy and salpingectomy, or oophorectomy or hysterectomy and both salpingectomy and oophorectomy; in 2 cases during salpingectomy and oophorectomy; in 1 case during tightening of the vesical sphincter, colporrhaphy, proctopexy and perineorrhaphy, and in 1 case during operation for excision of a sinus following cesarean section and freeing of adhesions to the uterus. The vesical wall was incised in 5 cases and torn in 3. Injury was detected at the time of operation in 7 cases and was not detected in 1 case; in these 7 cases, the wound was sutured, in 1 with drainage of the wound and in 1 with drainage of the bladder through a retention catheter. Convalescence was uneventful in 4 cases and prolonged in 3. Death resulted eventually from the vesical injury in 1 case as a result of bilateral pyonephrosis due to scar tissue obstructing the ureters following several attempts at repair of a vesicovaginal fistula.

Stevens concluded that infection of the urinary tract should receive appropriate treatment prior to operative procedures. The bladder and its attachments should be handled carefully during pelvic operations. Although no serious consequences follow repair of the vesical wall in the majority of cases, when injury is detected at the time of operation, exceptions to this rule are not uncommon. In cases in which drainage is used, convalescence is considerably shorter. Accidental operative injuries of the bladder are not infrequently responsible for prolonged convalescence, and they occasionally are fatal.

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41. Beer, Edwin: *Postoperative Suprapubic Fistula: Analysis of Causes*, Surg., Gynec. & Obst. **56**:959 (May) 1933.

42. Stevens, W. E.: *Female Bladder Injuries Incident to Surgery*, California & West. Med. **39**:388 (Dec.) 1933.

*Injury Following Irradiation.*—Dean<sup>43</sup> reported the cases of 47 women who were examined and treated for injuries of the bladder after irradiation of the uterus. Both radium and the roentgen rays were used, although by far the more intense radiation was delivered by radium. The primary uterine diseases comprised a number of conditions, both benign and malignant. Radiologic treatment varied within wide limits; it preceded the onset of urinary symptoms in the average case by two and a half years. Urinary symptoms consisted of frequency, dysuria and hematuria. Cystoscopic examination gave evidence of ulceration, anemic regions surrounded by intense inflammation or punctate hemorrhage. The lesion was situated in the posterior third of the vesical base in or near the median line. Diagnosis was based on the history and the results of vaginal examination, cystoscopy and biopsy. Treatment consisted of opiates for pain, lavage of the bladder with dilute phosphoric acid both transurethrally and by mouth, and instillations of mild silver protein and mercurochrome.

Dean concluded that when one employs the accepted methods of treating carcinoma of the uterus with high voltage roentgen rays combined with radium applied within the cervix or body, the vesical base, in some cases, unavoidably receives sufficient irradiation to cause ulceration. This possibility must be recognized by all physicians who treat uterine carcinoma. Vesical injury occasionally follows the application of comparatively light doses of irradiation to relatively insignificant uterine diseases. A woman who has reached the age when carcinoma is liable to develop, who suffers with frequency, dysuria and hematuria, and who presents on cystoscopic examination an ulcerated condition of the bladder, may have either vesical carcinoma or a tertiary reaction to irradiation. If an injury of the bladder due to irradiation is treated by irradiation, electrocoagulation, cauterization or by any of the other methods of treating carcinoma which are of a destructive nature, the results are disastrous. With proper management, however, the end-results are excellent in the majority of cases.

*Nerve Control.*—Mertz<sup>44</sup> stated that changes in the spinal cord resulting in disturbed nerve control of the bladder may be due to spina bifida occulta. Laminectomy, with freeing of the cord from pressure and traction, may relieve vesical symptoms. Laminectomy is justifiable in the presence of spina bifida occulta when chronic urinary retention with distention of ureters and pelvis coexists and no obstructive pathologic change is demonstrable. Laminectomy should not be carried out for enuresis alone, although definite spina bifida occulta exists, before

43. Dean, A. L., Jr.: Injury of the Urinary Bladder Following Irradiation of the Uterus, *J. Urol.* 29:559 (May) 1933.

44. Mertz, H. O.: The Relation of Spina Bifida Occulta to Neuro-Muscular Dysfunction of the Urinary Tract, *J. Urol.* 29:521 (May) 1933.

the patient has reached the age of puberty and then only after all other measures have failed. Mertz stated that of 6 patients who underwent laminectomy for spina bifida occulta, 2 were relieved of vesical symptoms and 2 gave evidence of slight improvement, whereas 2 obtained no appreciable relief from symptoms.

#### URETHRA

*Tumors.*—Counseller and Paterson<sup>45</sup> reviewed the literature and reported 12 cases of carcinoma of the female urethra. Four of the 12 patients were living five years after treatment, and those who died had an average duration of life of twenty-five and a half months; excluding 1 patient who lived six years, the average duration of life was sixteen months. The highest percentage of five year cures was obtained in cases in which radium and roentgen rays were used. Counseller and Paterson stated that obviously their series was too small to warrant conclusions with regard to results.

Lazarus<sup>46</sup> reported 3 cases of primary benign tumor of the urethra: 2 of the growths were papillomas and 1 was a fibromyoma. Among tumors of the urethra the polyps and papillomas represent epithelial tumors; the fibromyomas represent connective tissue tumors. Lazarus stated that polypi and cysts of the urethra are products of urethral inflammation rather than true neoplasms. Papillomas, although actual tumors, are frequently initiated by chronic inflammatory conditions within the urethra. Fibromas and fibromyomas are true neoplasms, the origin of which is not dependent on inflammation. The diagnosis of these tumors is usually made by inspection, either directly or through the cysto-urethroscope. Biopsy is frequently necessary for confirmation of the clinical diagnosis made by the eye. Lazarus said that the treatment consists of fulguration in cases of polypi, cysts or papillomas, or extirpation in cases of tumors of the connective tissue.

#### EPIDIDYMIS, SEMINAL VESICLES AND TESTES

*Torsion of Spermatic Cord.*—O'Connor<sup>47</sup> stated that most patients with acute torsion of the spermatic cord are seen first by their regular physicians who, as a rule, do not consider this condition in making a differential diagnosis. The diagnosis of orchitis, epididymitis or "acute hydrocele" is frequently made without proper correlation of history,

45. Counseller, V. S., and Paterson, Susanne J.: Carcinoma of the Female Urethra, *J. Urol.* **29**:587 (May) 1933.

46. Lazarus, J. A.: Primary Benign Tumors of the Urethra: Report of Three Cases, *Urol. & Cutan. Rev.* **37**:604 (Sept.) 1933.

47. O'Connor, V. J.: Torsion of the Spermatic Cord, *Surg., Gynec. & Obst.* **57**:242 (Aug.) 1933.

symptoms and physical signs. Since operative intervention results in conservation of the testis only when resorted to in the first few hours after the onset of symptoms, it is necessary that the diagnosis be made at the earliest possible moment.

Torsion may occur at any age; it has been recognized shortly after birth, and O'Connor stated that in one of his cases it occurred when the patient was 68 years of age. Probably it occurs more frequently during childhood and adolescence. Torsion of the spermatic cord has been observed more commonly on the right side and, in slightly more than half of the cases, in incompletely descended testes. It probably is brought about by contraction of the cremasteric fibers; there must be abnormal attachment of the testis and a certain deficiency in make-up of the gubernaculum associated with a more or less capacious tunica vaginalis. This anatomic variation would not cause torsion; the twist results from repeated contraction of cremasteric muscle bundles, strands of which may be anomalous. Therefore, the degree of torsion, that is, the number of half turns or full turns which the cord undergoes, depends indirectly on the freedom of the testis to be rotated inside the tunica and directly on the strength of the muscular contraction.

O'Connor stated that at operation the pathologic changes are characteristic. The cord above the twisted segment contains either dilated or flattened and partially obliterated spermatic veins depending on the extent of their occlusion in the twist. The spermatic artery is always greatly dilated but, usually, pervious. If the condition is acute, the surrounding tissue is edematous and, if chronic, it is adherent and fibrous. In acute cases, the twist occurs from without inward among more than two thirds of the patients. In the recurrent cases, no definite rule can be formulated. The extent of the twist varies from one-half turn to two full turns, and the site of the twist is always in that free portion of the cord which, covered by tunica vaginalis, suspends the epididymis and testis. O'Connor cited 9 cases, 5 of which were verified at operation, 3 by the observations and subsequent course and 1 by the obviously recurrent type of the condition with gradually developing atrophy. Orchitis, as a clinical entity, except in association with epidemic parotitis, is an uncommon condition, and the term should not be loosely applied to explain undifferentiated scrotal swellings. Bearing in mind the characteristic sudden onset of torsion, with the more or less typical local signs, will permit an early diagnosis to be made with immediate operative detorsion, which is necessary in most acute cases if testicular tissue is to be conserved.

*Spermatocystitis.*—Valverde<sup>48</sup> stated that in refractory cases of chronic spermatocystitis the only satisfactory treatment is the heroic

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<sup>48</sup>S. Valverde, Belmiro: Le lavage des vésicules dans le traitement des spermato-cystites chroniques, J. d'urol. 36:262 (Sept.) 1933.

one of lavage of the vesicles, either by means of Belfield's vasotomy or by the vasopuncture of Luys. Valverde prefers the latter, as it is simpler and gives somewhat better results. Lavage is done under local anesthesia with procaine hydrochloride or nupercaine, each vesicle receiving an injection of from 10 to 12 cc. of a 5 per cent solution of colloidal silver. In 8 of the cases there was a complication of simple funiculitis, which healed spontaneously. Valverde reported good results. The method can always be used successfully except when intrapelvic obstructions exist; under such conditions, the liquid cannot reach the vesicles and lavage must be done through the ejaculatory ducts by urethroscopic catheterization. Records of Valverde's service revealed 340 patients with chronic spermatoecystitis among the 1,200 patients of this private clinic, and 452 patients with this condition among 2,800 patients with genito-urinary disease at the General Polyclinic of Rio de Janeiro. The technic is simple, though it demands great care: The isolation of the vas must be complete and careful to the last degree, pains being taken to liberate it from all sheaths and adhesions. When, however, there is obstruction, the procedure is more difficult; the vas must then be isolated over a distance of from 10 to 12 cm. in a search for a nonobstructive point. Puncture should be made in the middle of the canal, the hand of the operator following its direction rigorously. The injection must be made immediately, as soon as the resistance of the wall is overcome by the entrance of the needle. Absolute rest in bed must follow the procedure, with opiates administered for three days. The drain is removed on the fourth day, and the patient gets up. Elimination of the colloidal silver is rapid for the first few days. Chronic spermatoecystitis transforms the seminal vesicles into foci of infection capable of harboring the infection for years.

#### UROGRAPHY

Swick<sup>49</sup> proposed sodium ortho-iodohippurate (hippuran), a halogen derivative of a compound normally found in the urine of man, as a medium for excretion urography. On the basis of its use in more than 200 cases, Swick has found the substance to be nontoxic, highly soluble and neutral in solution, and to yield satisfactory urograms. He stated that it possesses 38.8 per cent of iodine in stable organic union. Iodism has never been observed. Generalized warmth and, occasionally, nausea and vomiting of very transient duration have been the only reactions noted. Thrombosis at the site of injection has not been observed. The compound is well tolerated and may be recovered from the urine as the insoluble acid. Rabbits were found to tolerate from 2 to 2.5 Gm. of substance per kilogram of body weight, administered intravenously

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49. Swick, Moses: Excretion Urography, J. A. M. A. **101**:1853 (Dec. 9) 1933.

in approximately 30 per cent concentration over a period of about ten minutes. Normally, from 90 to 95 per cent is excreted within eight hours after injection, from 60 to 66 per cent during the first hour and from 70 to 80 per cent during the first two hours. A solution of this substance remains unchanged in color or reaction after sterilization or on standing, and it may be prepared and distributed in sterile vials ready for use.

Swick stated that, for adults, a dose between 10 and 15 Gm. of this substance dissolved in distilled water, in approximately 50 per cent concentration, has been used. The injection should take about five minutes; the first exposure should be made about ten minutes later, and two subsequent exposures at twenty minute intervals. In cases of functional derangement, particularly in the presence of obstructive conditions, additional films are indicated to determine definitely the absence of visualization or the presence of late visualization.

Swick stated that oral administration in man has also yielded satisfactory results. Of 25 cases, in approximately 50 per cent good diagnostic urograms were obtainable from ninety to one hundred and thirty-five minutes after administration. From 10 to 15 Gm. of the substance dissolved in approximately 75 cc. of simple syrup was given by mouth. No reactions were noted. The only subjective sensation recorded was the salty, aromatic taste of the solution. Forty-five minutes after taking the solution, the patient is placed on the urographic table, a moderate degree of compression is applied, and exposures are made sixty, ninety, one hundred and twenty and one hundred and fifty minutes after ingestion of the substance. Swick stated further that, in order to obtain clearly defined and readable excretory urograms, it is important to apply a moderate degree of compression over the region of the urinary bladder by means of an air-inflated balloon held in place by the canvas sheet of the compressing apparatus.

Braasch<sup>50</sup> stated that excretory urography should and will be employed as a routine in the diagnosis of abdominal lesions. He said that its greatest handicap at present is in interpretation, but that this will become so standardized as to permit the method to be more generally employed. Its greatest value will be in determining the presence of stasis in the renal pelvis or ureter, in interpreting shadows in the upper part of the urinary tract and in giving fairly accurate estimates of renal function. Braasch also stated that it will always be an invaluable aid to the urologist in conditions in which cystoscopy and ureteral catheterization are impossible or inadvisable. It should be of help in determining the necessity for surgical treatment of renal ptosis. The data afforded

<sup>50</sup> Braasch, W. F.: The Practical Application of Excretory (Intravenous) Urography, J. A. M. A. **101**:1848 (Dec. 9) 1933.

by this routine procedure should be complementary to other urologic data, and in only a limited field will it entirely replace former data.

Ravasini<sup>51</sup> stated that intravenous urography or, more correctly, urography by excretion of a shadow-giving or contrast substance, is an addition to the diagnostic resources in urology. Coincident with the use of the newer preparations, the inconveniences and accidents of the older ascending or retrograde method have been overcome. In the majority of cases, the newer methods give information not only as to pathologic changes in the kidney, but also as to any alteration in its functional capacity. The detailed observations of Ravasini were based on 1,000 of his cases in which intravenous urography was employed. In addition, an analysis is made of a large number of cases reported by other Italian and many foreign urologists. Ravasini has studied the behavior of the normal and pathologic kidney in eliminating the contrast medium, nephrography and the appearance and intensity of shadows and factors which show the relation between the intensity of the shadow and functional capacity of the kidney. He also studied the peristaltic movements of the renal pelvis and ureter and the manner in which intravenous urography yields valuable information as to both the anatomic and the physiologic condition of the ureter.

Ward<sup>52</sup> has had experience with pyelography by the descending route, or excretion urography, since 1929, and he has tested such chemical products as have generally been available for the purpose. Patients suffering from certain diseases are generally recognized as being unsuitable for investigation by this method. In the great majority of other cases, the method appears to be harmless, but on general principles it would seem wise not to use it repeatedly on the same person. It can be employed safely for children, and its value here is obvious, as also in many other conditions in which catheterization of the ureters is impossible. With very small infants, it is difficult to obtain shadows of sufficient density for diagnostic purposes. Ward stated that descending pyelography is a method of investigation that never fails to give valuable information when any disease of the kidneys and ureters exists. By means of this method, the health of these organs can often be established with great precision. It is also of use, although to a lesser extent, in the investigation of some vesical conditions. It does not replace ascending pyelography; the two are distinct and each has its own peculiar value. The former can almost always be employed; it gives information

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51. Ravasini, Carlo: *Pielografia per via discendente*, Fifth Cong. Internat. Soc. Urol., 1933, p. 315.

52. Ward, R. O.: *Pyelography by the Descending Route, Otherwise Known as Excretion Urography, or Intravenous Urography*, Fifth Cong. Internat. Soc. Urol., 1933, p. 356.

of the greatest value concerning the physiologic condition of the kidneys and ureters and, in the majority of cases, depicts clearly their anatomic condition as well; but the latter reveals even better the anatomic details of renal cavities and has the advantage that specimens of urine from each ureter can also be collected. However, its employment is not always possible. Excretory urography makes it possible to study the activities of the kidneys and ureters while they are in an entirely undisturbed condition, and one which is physiologic except for the stimulus to secretion which occurs as a result of injection.

Ward stated that when partial stasis exists the most intense shadow usually develops after thirty minutes. Faint and varying shadows in the kidney and ureters which appear and fade away early indicate health. Dense shadows of constant form are not normal; they indicate a capacity to secrete, but a disorder in the conductive mechanism, and when late in appearance they give proof of impairment of the first of these two functions alone. A healthy ureter is never found filled with opaque fluid throughout its whole length at one time, the one exception to this rule being the ureters of the female during pregnancy. After his extensive study of this procedure, Ward stated that descending pyelography has given an even greater contribution to urology by the manner in which it makes visible the actions of the ureters in health, and that when the ureters are diseased it always reveals this condition; moreover, the results of operation on them and on the renal pelvis can be determined as was never before possible.

#### LYMPHOGRANULOMA INGUINALE

Cole<sup>53</sup> stated that lymphogranuloma inguinale is a distinct granulomatous entity involving the lymph nodes. After an incubation period of from one to several weeks, not necessarily accompanied by a primary sore, there results a chronic condition with the formation of buboes which eventually suppurate. The lymph nodes around the lower portion of the rectum may be involved, the inflammatory reaction often resulting in strictures of the rectum. Cole said that the cause of lymphogranuloma inguinale is a filtrable virus which can be transferred to several of the lower animals. He stated that a specific diagnostic cutaneous reaction (Frei reaction) has been evolved, the emulsion material from unbroken involved nodes being used as antigen. Cole stated that patients with buboes who are seen early respond comparatively well to surgical excision of the involved nodes or to intravenous injection of a solution of antimony and potassium tartrate. This disease, he says, is by no means rare in America.

<sup>53</sup> Cole, H. N.: Lymphogranuloma Inguinale, the Fourth Venereal Disease: Its Relation to Stricture of Rectum, *J. A. M. A.* **101**:1069 (Sept. 30) 1933.



## CAUDAL ANESTHESIA

Campbell<sup>54</sup> stated that the results of caudal anesthesia in 83 boys parallel the observations of others in larger series of adults. In 67 (80.7 per cent) cases, anesthesia was satisfactory, which means that instrumentation was painless; in 7 (8.4 per cent), it was partially satisfactory, instrumentation having been performed with some discomfort. Campbell stated that the indications for, contraindications to and the administrative technic of caudal block are fundamentally alike for children and for adults. Among a great many children the employment of caudal block will eliminate general anesthesia. This is particularly desirable when the question of anesthesia delays or forbids the early establishment of the correct diagnosis and the institution of adequate treatment. In this group, the ease of administration and the results strongly recommend caudal block.

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54. Campbell, M. F.: Caudal Anesthesia in Children, *J. Urol.* **30**:245 (Aug.) 1933.

## REMOVAL OF CEREBELLOPONTILE (ACOUSTIC) TUMORS THROUGH A UNILATERAL APPROACH

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BALTIMORE

For the attack on the well recognized encapsulated tumors of the cerebellopontile angle (erroneously, I think, called acoustic tumors) the bilateral cerebellar approach has been adopted by all neurosurgeons. I know of no exception to this rule. The purpose of this communication is to present a radical departure from this standardized approach, namely, to offer in its stead, a unilateral exposure, essentially similar to that now used when the fifth, eighth and ninth nerves are divided for various symptoms referable to these nerves.

Originally a unilateral approach was proposed by Krause; it was used by others and subsequently given up because it was entirely inadequate. A pertinent query is, therefore, Why again propose a seemingly similar approach which has been proved to have disastrous consequences? The answer is that new developments, particularly methods of space reduction, then not known or not properly appreciated, now offer all of the advantages obtained by the more extensive exposure. It is well known to those who have had much experience with these tumors that the patient's resources may be so severely taxed by the bilateral approach alone, particularly with the bloody midline, that the additional attack on the tumor at the same operation may be inadvisable. For many years surgeons, at least those in this country, have used the tremendous exposure provided by the so-called cross-bow incision of Cushing. Perhaps a decade ago, I gave this up for the more simple, less bloody and less arduous transverse incision, which is curved downward at the mastoid processes. This provides the same exposure and makes the approach to the angle easier, because the big nuchal muscles fall away from, rather than toward, the line of vision. Moreover, the cerebrospinal fistulas that developed all too frequently in the vertical part of the cross-bow incision, with many disastrous sequelae, were automatically avoided. The transverse incision which I<sup>1</sup> employed was much like that

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<sup>1</sup> Dandy, W. E.: An Operation for the Total Removal of Cerebellopontile (Acoustic) Tumors, *Surg. Gynec. & Obst.* 41:129, 1925. Cerebellopontine (Acoustic) Tumors, in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1933, vol. 12, chap. 1, p. 534.

proposed by Cotterill<sup>2</sup> in 1899, but it was modified by enlarging the cutaneous incision and bony defect upward and outward on the side of the tumor. Gradually the conclusion was forced on me that, after the other items in space compensation had been put into effect, the bilateral bony defect was really contributing little, if anything, to the relief of pressure in the posterior cranial fossa. In further simplification, therefore, the unilateral cerebellar approach is now proposed. It has been used in the last four tumors of this character and with no less satisfactory exposure of the tumor than with the bilateral approach. Unquestionably nothing can be worse than attempting to remove a tumor of the brain without providing adequate room not only for the existing intracranial pressure and the approach to the tumor but for all postoperative edema that develops. But it is also clear that all superfluous room is obtained at the cost of the patient's none too great physical reserve. If it is necessary to choose between too little and too much room, there can be no argument concerning the choice of the latter, but the best results are always obtainable by making the smallest approach that satisfies all needs. It will therefore be understood that, in suggesting the unilateral approach for cerebellopontine tumors, it is done with the full realization that inadequate provision for room is disastrous.

I might also add that obtaining room in the standardized fashion through a bilateral cerebellar decompression is in itself frequently most injurious to the contents of the posterior cranial fossa, i. e., the cerebellum and brain stem. I have in mind the great thrust backward of the cerebellum and brain stem when the dura is widely opened. The result of this is seen in the cerebellum, which is swollen from edema and internal hemorrhages and, symptomatically, from the patient's altered pulse and respirations. It is my feeling that many postoperative deaths are due to this injury inflicted early in the operation. By the unilateral approach only the outer part of the cerebellum on the operative side can be extruded, and this part is excised in preparation for the exposure of the tumor.

#### REDUCTION OF PRESSURE WITHIN POSTERIOR CRANIAL FOSSA

How, then, is the increased pressure within the posterior cranial fossa reduced to the point of safety?

*Avertin Anesthesia.*—First and perhaps most important is avertin anesthesia. Although the contents of the posterior cranial fossa are always under high pressure from three factors—(a) the tumor itself, (b) the internal hydrocephalus and (c) contiguous edema of the cerebellum and brain stem—an additional amount of pressure of variable but always important degree resulted when ether was used as an anesthetic. The absence of this effect with avertin has been commented

2. Cotterill, J. M.: Remarks on the Surgical Aspects of a Case of Cerebellopontine Tumor by Bruce, Tr. Med.-Chir. Soc., Edinburgh 18:215, 1898-1899.

on elsewhere. It has greatly reduced the hazards of all operations for tumors of the brain and has also permitted the exposure of tumors by such smaller cranial defects. In hypophyseal tumors, for example, the opening in the bone is now one third or less than was required when ether was in use. The proposal to reduce the cerebellar approach to approximately one third of the former amount is only in keeping with the improvement made possible in hypophyseal operations. Without avertin as an anesthetic, the methods of space reduction that follow would doubtless be insufficient.

*Tapping of a Lateral Ventricle.*—When a lateral ventricle is tapped until the ventricular fluid ceases to flow, the supratentorial pressure is reduced to that of the atmosphere (fig. 1). This procedure, probably first introduced by Krause of Berlin, greatly relieves the pressure in the posterior cranial fossa. It is now quite generally used by surgeons in all operations for tumors below the tentorium. Without it all cerebellar operations would be dangerous when a high degree of pressure obtains. By gentle and steady pressure on the exposed dura an additional amount of fluid is obtained from the lateral ventricle, and in exactly this amount the subtentorial pressure is still further reduced. The latter method of relief must be used with great caution, for the pressure is likewise on the medulla, which above all else must not suffer. It might be added that in the unilateral approach the pressure is exerted more directly on the tentorium and less directly on the medulla than when all of the bone is removed in the bilateral exposure. Rather than incorporate the ventricular openings in a high occipital incision, as many operators prefer, I make two independent horizontal incisions (fig. 1 *A*), exactly as for ventriculography. By so doing the transverse incision can be made very low, i.e., below theinion, and a big, overhanging cutaneous flap can thus be avoided.

*Evacuation of Fluid from the Cisterna Magna and Spinal Canal.*—In nature's efforts toward space compensation for tumors in the posterior cranial fossa, the cerebellar tonsils are usually forced into the spinal canal, thus obliterating the cisterna magna entirely or in large degree. It might appear that this source of room, i.e., obtained by evacuating the fluid in the cisterna magna, which is of such great service in attacking the cranial nerves, would then be denied the operator on cerebellopontile tumors. The membranous roof of the cisterna is more difficult to reach, and the evacuation of the cisterna is not so spontaneous after it has been opened, but by gentle retraction on this part of the cerebellum the arachnoidal covering can be pricked and the tonsil elevated sufficiently (fig. 1) to permit the release of a large amount of fluid with proportionate covering of the pressure below the tentorium.

*Excision of the Outer Cap of the Cerebellum.*—This procedure is important in two ways: (*a*) It still further reduces any excess pressure within the posterior cranial fossa, and (*b*) the tumor is

exposed so that it may be attacked directly, i. e., without elevation of the cerebellum. Additional items of importance are (c) that postoperative edema of the cerebellar lobe from traction is avoided, and (d) that ample room is provided for any degree of postoperative edema that may ensue (fig. 1).

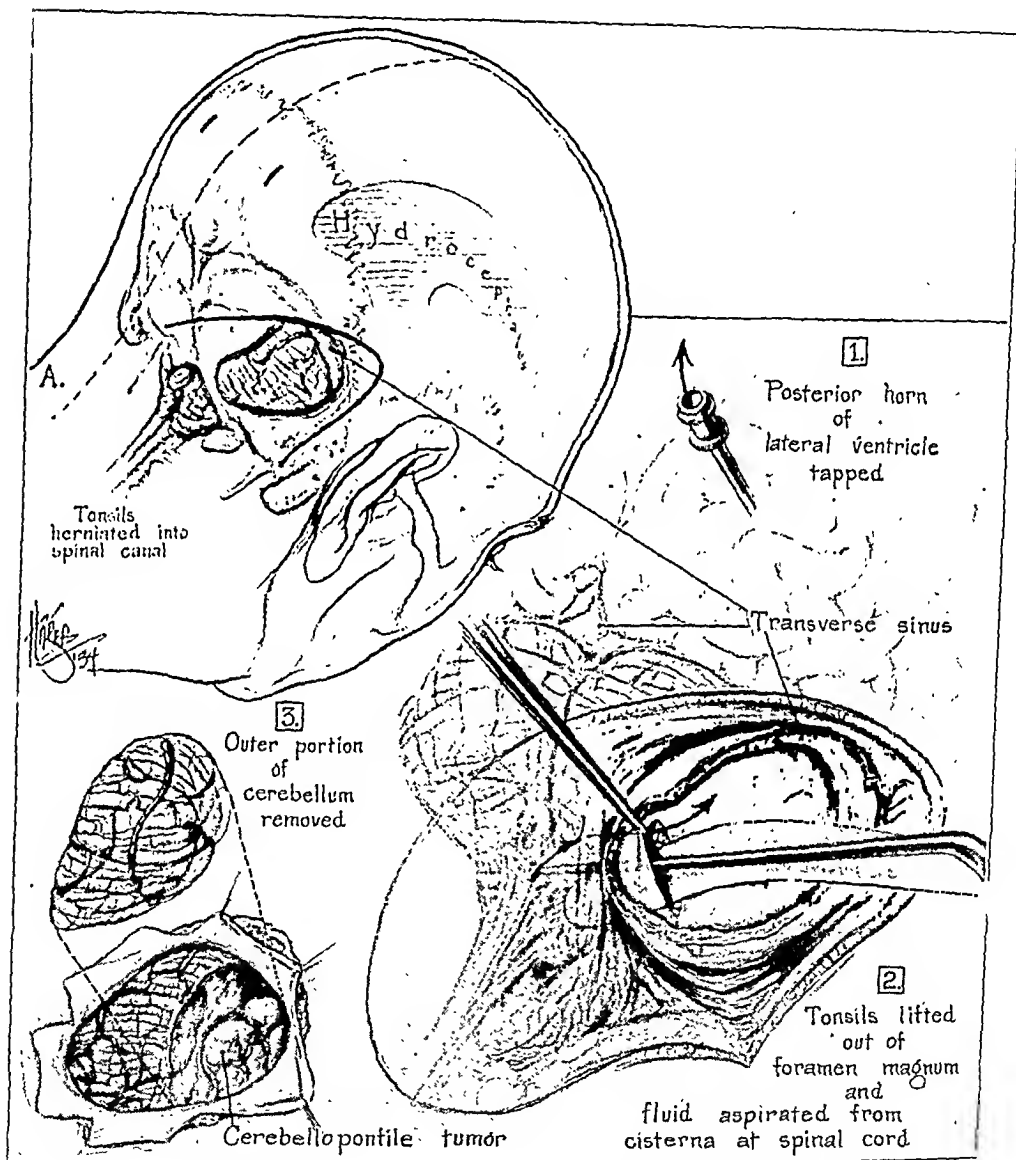


Fig. 1.—A, the relative exposure used in the removal of cerebellopontile tumors by the unilateral approach; 1, the method of releasing the supratentorial pressure by puncture of the posterior horn of the lateral ventricle; 2, further release of pressure in the posterior cranial fossa by evacuation of the cisterna magna in the spinal canal; 3, final stage by the resection of the outer cap of the cerebellum.

Apparently there are no permanent effects from removal of this part of the cerebellum, the weight of which averages about 15 Gm. (fig. 4).

First suggested by Frazier<sup>3</sup> (1905), this method was rather harshly criticized at the time and until recently gained only a few adherents. It is an essential part of the unilateral operation. Cerebellopontile tumors can be removed by the bilateral operation without excision of the outer cap of the cerebellum, but even then to remove it makes the operation easier and the risk to life and function less. With the unilateral approach, removal of the tumor could hardly be attempted without this expedient. For its success the unilateral approach is indeed dependent on all of the methods of space reduction. It has been used in the last

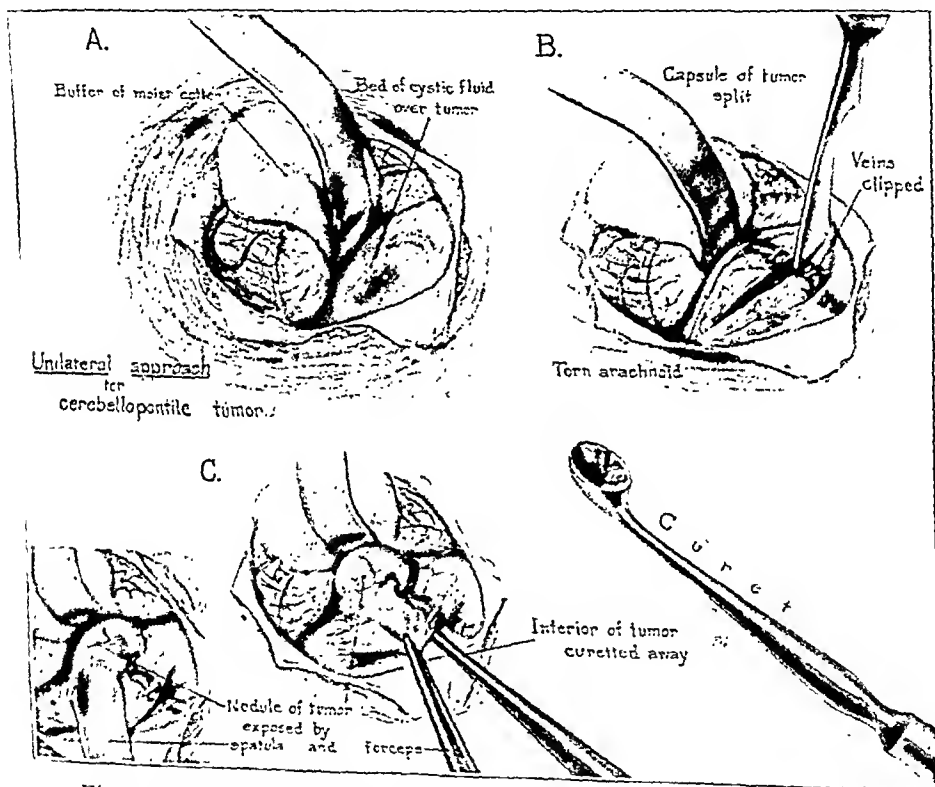


Fig. 2.—The method of attacking the tumor after the reduction of the intracranial pressure: *A*, exposure of the tumor; *B*, splitting the capsule of the tumor preparatory to intracapsular enucleation, and *C*, the gradual withdrawal of the capsule from its bed.

four cases, in each of which the tumor was totally removed according to the method of attack described elsewhere (figs. 2 and 5). For the past ten years I have strictly adhered to the policy of totally removing all tumors of this kind when seemingly possible, being firmly convinced that the operative mortality is not greater than by the partial removal and

<sup>3</sup> Frazier, C. H.: Remarks upon the Surgical Aspects of Tumors of the Cerebellum. *New York M. J.* 81:272 and 332, 1905.

that the postoperative course is smoother and more secure; never have I seen recurrence of such a growth as must always obtain when the interior of the tumor is removed. Three of the patients operated on by the unilateral approach are living and well. One of these was a decrepit woman, aged 62. Had a bilateral operation been performed, complete extirpation of the tumor would hardly have been possible. The last patient, who died, had the largest tumor of this type that I have seen (66 Gm.). She was comatose and badly dehydrated and had long

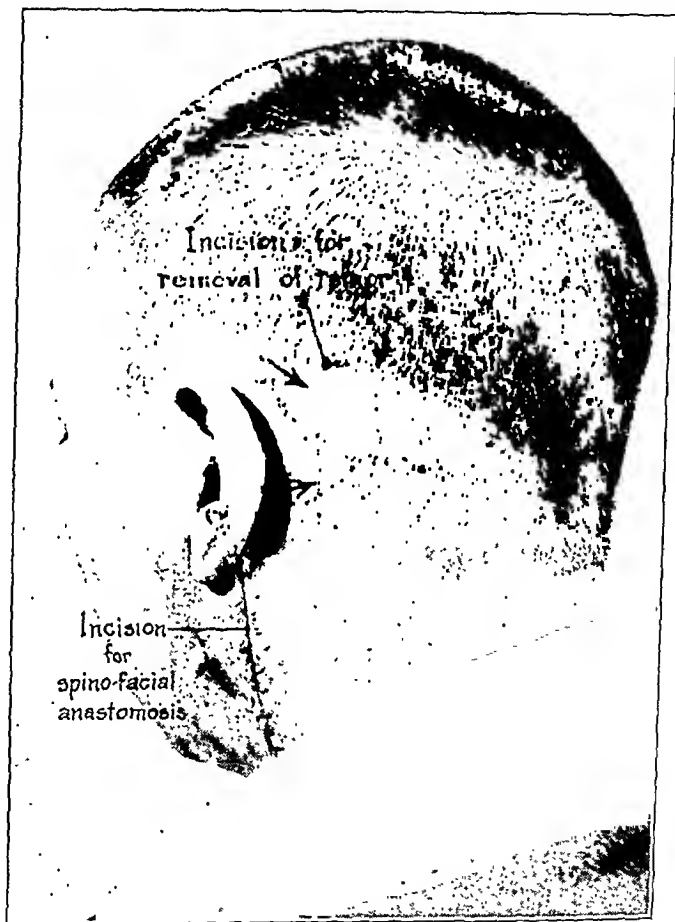


Fig. 3.—The operative scar following the removal of the acoustic tumor by the unilateral approach. Ten days after the tumor's extirpation a spino-facial anastomosis was made by an incision in the neck.

been blind. Earlier experiences were sufficient to prove that she could not survive a bilateral operation with complete removal or only partial extirpation. Up to the present comatose patients with cerebellopontile tumors have presented an insuperable problem. Perhaps with smaller tumors the unilateral approach may offer a degree of hope. Even with a tumor of this size the operative attack was at no time handicapped by lack of room or by intracranial pressure.

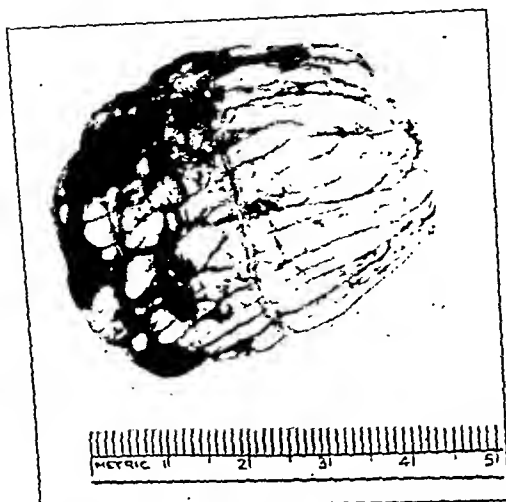


Fig. 4.—The outer cap of the cerebellum removed preparatory to the excision of an acoustic tumor which weighed 15 Gm.



Fig. 5.—Fragments of the interior tumor were removed with the curet, after which the remaining nubbin (the largest fragment) was gently withdrawn from its bed in the pons.



It cannot be claimed from this small series that a bilateral approach may never be indicated; certainly the need for it would appear to be exceptional. If the dural pressure is excessive after the release of ventricular fluid, one can continue the incision into the bilateral form without loss. The only difference between the unilateral approach used in trigeminal neuralgia or Ménière's disease and that in tumors of the cerebellopontile angles (fig. 3) is that the bony defect is increased somewhat toward the foramen magnum (fig. 1) in order to expose the restricted cisterna magna more easily, and toward the tentorium so that any tentorial vein may be safely thrombosed and divided when the cap of the cerebellum is being excised.

# MYOKINETIC STUDIES OF TRANSPLANTED MUSCLES ABOUT THE KNEE

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CINCINNATI

It is the purpose of this paper to present an accurate method of studying muscular contraction and its significance to gait in the normal person and after transplantation of muscles. The principles of these studies are found in Dr. Arthur Steindler's comprehensive lectures on myokinesiology and the work of Dr. R. Scherb. I shall briefly review the anatomy and physiology of the muscles of the thigh and outline the myokinesiology of the knee and the structures about it. These subjects are intimately related and are essential for an adequate discussion of transplantation of tendons. I have designed an instrument, the myokinesiometer, for the purpose of accurately recording muscular action in gait. The record obtained with the myokinesiometer shows the time and the extent of muscular contractions as compared with various phases of gait. I believe that the findings can be applied to orthopedic surgery, especially in cases of muscular imbalance as found in infantile and spastic paralysis. The myokinesiometer can be used for the examination of the majority of the muscles of the extremities. I have examined a series of normal persons and have compared my findings with those of Scherb. I have also examined a series of patients who have had transplantation of a tendon in the thigh. Observations were made to determine the action of the transplanted muscle and whether or not its action changed in relation to the gait after transplantation.

## ANATOMY

In spite of the fact that the knee joint is large and has a large range of motion, it is remarkable for its stability. The large condyles of the femur articulate with the condyles of the tibia. The condyles are separated by two semilunar cartilages designed to produce a larger range of motion. The inner cartilage is C-shaped; its anterior and posterior horns are separated widely from each other in the midline; its posterior one half is firmly attached to the capsule; its anterior portion is attached near the crucial ligament and the anterior articular surface of the tibia. The external cartilage is circular; its two horns come closely together in the midline of the joint; it is not so firmly attached as the inner one,

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From the service of Dr. Arthur Steindler, department of Orthopedic Surgery, University of Iowa, Iowa City.

and consequently it allows for a greater freedom of motion. These cartilages divide the joint into an upper and a lower half. The entire joint, including the patella, is enclosed in a large capsule. The capsule extends up on the anterior aspect of the femur to form a large pouch. The capsule is lined with synovia, which projects into the interior of the joint, anteriorly and posteriorly. The ligamentum mucosum and ligamentum alare are formed by the projection of prepatellar fat backward into the joint, which carries the synovia before it. The crucial ligaments push the synovia forward from the posterior aspect of the joint. The crucial ligaments are situated in the intercondyloid space.

The posterior crucial ligament runs from the posterior tibial spine to the median portion of the intercondyloid notch. The anterior crucial ligament runs from the anterior tibial spine to the lateral part of the intercondyloid notch. The anterior crucial ligament is longer than the posterior one. These ligaments aid in the stability of the knee by checking certain motions in all positions of the knee. The anterior crucial ligament becomes taut in extension, and the posterior crucial ligament becomes taut in extreme flexion. The lateral ligaments aid more in the stability of the knee than do the crucial ligaments.

On the anterior aspect of the thigh in the region of the knee is the quadriceps femoris. This muscle comprises a group of four: the (1) rectus femoris, (2) vastus lateralis, (3) vastus medialis and (4) vastus intermedius. The four muscles converge toward the patella and are inserted into the tubercle of the tibia. The patella is a sesamoid bone in the quadriceps tendon. Immediately above the knee the rectus femoris is superficial. The vasti lie on either side, and the vastus intermedius envelops the femur and is concealed by the other muscles. The rectus femoris has a double tendinous origin: (1) the straight head arises from the anterior inferior spine of the ilium, and (2) the reflected head arises from a rough groove on the dorsum ilii just above the highest part of the acetabulum. The vastus medialis arises from the distal two thirds of the linea aspera. The vastus intermedius arises from (1) the proximal two thirds of the body of the femur on the anterior and lateral surfaces and (2) the distal one half of the linea aspera.

The sartorius has its origin at the anterior superior spine and is inserted into the tibial tubercle.

The semitendinosus arises from the ischial tubercle and is inserted (1) into the medial side of the body of the tibia just distal to the medial condyle and (2) into the deep fascia of the leg.

The semimembranosus arises from the superior and lateral facet or the ischial tuberosity and is inserted into the horizontal groove on the posteromedial aspect of the medial condyle of the tibia.

The biceps femoris arises by its long head from the inferior and medial facet on the sciatic tuberosity and from the sacrotuberous liga-

ment. The short head arises from (1) the entire length of the lateral lip of the linea aspera and the proximal two thirds of the lateral epicondylar line of the femur and (2) the lateral intermuscular septum. The muscle is inserted into the head of the fibula.

The gracilis arises from the inferior ramus of the os pubis and is inserted into the medial surface of the body of the tibia just distal to the medial epicondyle.

In the cases studied in this report, the following principles of transplantation of tendons have been carefully observed:

1. Deformities should be corrected before transplantation by the breaking up of the adhesions and the severing of ligaments by means of a wedge resection or other operative procedure.

2. The mechanical arrangement of the transplanted tendon must be such that a straight line of pull is efficient, and the tendon acts in full force on its point of application.

3. All of the slack of the tendon should be taken up by applying sufficient tension when the joint is in the position of correction.

4. The anchorage of the tendon is important. The periosteal attachment is preferable to the tendon attachment.

5. The transplant should not be in contact with a bony surface, nor should it pass through a small hole in a fascial septum, because it will become adherent and interfere with movement.

6. The patient should be reeducated in the use of the transplanted muscle in its new position, or it may not function.

7. The choice of the proper muscle to be transplanted cannot be overemphasized. In acquired deformities the responsible cause is of significance whether it is spastic paralysis, infantile paralysis, partial paralysis, a stretched or contracted muscle or only a loss of muscular tone. With few exceptions, one group of muscles is paralyzed without other groups being affected.

Certain aspects of the function of muscle obviously concern transplantation, especially in its relation to kinetics. The function of the muscles depends to a large extent on the size, shape and direction of the muscle fibers as well as on the shape and length of the involved bones. The muscles have physiologically adapted themselves to physical requirements, such as speed and strength. The long, narrow muscle is adapted for speed, whereas the short, thick muscle is built for strength. Muscular action is modified further by various mechanical arrangements of the lever arm of the muscle, i. e., by changing the perpendicular distance from the point of application to the center of motion. Provided all of the other factors remain equal, a muscle will be capable of greater speed per unit of contraction if the muscle is attached close to

the joint. There is an example of this fact in the flexors of the knee. The flexors run parallel to the femur, and they are deflected in their course as they pass the posterior portion of the condyles of the femur. The lever arm of the muscles is changed because the condyles project considerably backward, and the tendons necessarily take on a much more diagonal direction just before the point of application of the leg is reached. In the case of the quadriceps femoris a sesamoid bone (the patella) is incorporated in its tendon, which makes a larger angle of application.

Muscles are arranged to work in groups, and the motion of the joint is dependent on normal functioning musculature. In the course of a muscle more than one joint may be involved. The hamstrings are polyarticular because they span the hip and the knee joints. The vasti muscles are monarticular, as they act on only the knee joint. The gastrocnemius is a polyarticular muscle arising from two heads, one on either side of the femur above the condyles. The muscles about the knee joint are long because they must accommodate the large range of motion of the knee, for the individual muscle fiber is able to contract only from one fourth to one half of its length in the relaxed position. In the upright standing position the knee joint maintains a position of inward rotation of 25 degrees against the head and neck of the femur and of 30 degrees against the lower end of the tibia. The normal range of motion is about 130 degrees, i. e., 50 degrees of flexion to from about 180 to 186 degrees of extension. Flexion and extension take place in the sagittal plane. In certain positions, the knee has a few degrees of inward and outward rotation.

Active insufficiency of the flexors of the knee joint as well as passive insufficiency of the quadriceps usually limits flexion. These conditions of the muscles are of importance in that they may influence treatment. The actual state of the muscle is accurately determined by myokinesio-graphic investigations.

The quadriceps muscles are essentially the only extensors of the knee joint. This action is chiefly accomplished by the vasti muscles. The tensor fasciae latae assists. The rectus femoris is not able to accomplish full extension under ordinary conditions. The extensor quadriceps is one of the most important stabilizers of the knee. When the knee is forcibly extended, the patella is drawn strongly upward by the quadriceps. The synovial lining and the fringes adhering to it are pulled out of the way of the condyles to prevent impingement. In this extended position the quadriceps muscles aid in stabilization. The anterior capsule is too large and loose to do so. The lateral ligaments of the knee assist greatly in the stabilization of this joint in extension because their posterior part becomes taut in this position: Abducent and adducent

movements of the tibia against the femur are checked by the lateral ligaments. These ligaments also check rotation when the knee is in extension, but when the knee is in flexion the lateral ligaments relax, and rotation is possible. During flexion the points of insertion of the lateral ligaments in the tibia and femur move closer together as the femur glides over the tibia. The lateral ligaments as well as the posterior capsule become loose, and rotary motion is possible. Rotary motion necessarily follows extension and flexion of the knee. In the beginning of flexion, the tibia is inwardly rotated against the femur. In extension the tibia is rotated outward in relation to the femur. In gait this is the case, for when the heel is placed on the ground, the pelvis swings forward, necessitating inward rotation of the thigh, for the foot cannot rotate while it is firmly planted on the ground. Naturally, if the femur is rotated inward, the tibia is rotated outward in relation to the femur. The inward rotation of the femur is primary, and the outward rotation secondary.

The action of the various muscles of the thigh is interesting, and a careful consideration of them is appropriate in this study. The action as compared to certain phases of gait will be considered later.

Contraction of the quadriceps tightens not only the tendinous insertion, pulling the patella upward, but also puts on tension of the entire anterior reenforcing apparatus of the knee, and thus aids considerably in the stabilization of the knee. The strength of the quadriceps is three times that of the combined hamstrings.

The hamstrings flex the knee joint, but they can extend the joint if the leg is fixed and the pelvis is free to move upward, causing the thigh to be extended against the leg.

The biceps act with a greater arm than do the inner hamstrings. The significance of this fact is that by so doing their action prevents a lockage of the knee when it is in full extension. Such lockage of the knee would occur if both muscles ran near the axis of the joint, in which case little or no rotation would develop in the muscles. The tendons of the hamstrings are inserted posteriorly, laterally and medially to the joint. The inner hamstrings rotate the knee inward. The outward rotation is accomplished chiefly by the tensor fasciae. These muscles must work with the utmost cooperation and efficiency. When one muscle contracts, its antagonist must relax. The relation of the actions of synergistic and antagonistic muscles are graphically illustrated by this myokinetic study. Scherb agrees with Codvilla in that the reciprocal action of the antagonists is controlled by the purpose of motion at the time of action. When a muscle is paralyzed, an interruption of the wave is experienced, and a transplantation is necessary to fill the gap. If the transplanted muscle takes the place of a synergist, it takes on a

synergistic action. A muscle may also be transplanted to take on the action of an antagonistic muscle. The opposite antagonist and agonist remain locked. One cannot take the place of another; they cannot fill their new function, which is strange to them in every phase of motion. It is evident that transplants depend not only on the mechanical and anatomic situations but also on the central nervous system. The myokinesigram can demonstrate when a muscle takes on not only a new function but a compensatory action.

It is interesting and instructive to note that in the movement of any part of the body, in order to have proper coordination, the contraction of the muscles or group of muscles is regulated by two sets of stimuli: (1) those arising within the fibers producing the contraction, and (2) those arising in the fibers of the antagonist group which is supposed to relax the latter, in that way giving the former group the power to function properly. For instance, when the extensors of the knee contract, messages pass from their muscle spindles, not only to the quadriceps motor cells, but also to the motor cells which control the opponent group of muscles, the hamstring flexors. If there is to be no loss of power, the work of the opposing groups must be coordinated with the utmost nicety.

#### MYOKINETIC DATA

The choice of the distribution of muscular power by transplantation of a tendon should be made by kinetic investigation. This investigation must be accurately made, thereby determining the absence of individual muscles or muscular deficiency. A myokinetic study is necessary to obtain this required knowledge of muscular action of the lower extremities in relation to the action of these muscles to certain phases of gait. In studying myokinetics from a clinical standpoint, the principles of inspection and palpation are followed.

I have attempted to facilitate these observations by devising an instrument which I have named the myokinesiometer, constructed as follows:

The myokinesiometer makes use of the principle employed in the microphone button of a radio. A similar button was made for my purpose by using a small brass pill-box  $1\frac{1}{2}$  inches (3.81 cm.) in diameter and  $\frac{1}{2}$  inch (1.27 cm.) deep. A hole, 1 inch (2.54 cm.) in diameter, was made in the top of the box, and a mica window was placed inside. The mica window accommodates considerable motion and does not conduct electricity. A large flat copper terminal, 1 inch in diameter, was placed in both the top and the bottom of the box, with a terminal attached to the center of each. The terminals projected through the top and bottom of the box. The box was then filled with granulated carbon and closed. It was mounted on a small, light steel frame. Elastic bands, 18 inches (45.72 cm.) long, were muscles of the thigh. A lever, 6 inches (15.24 cm.) long, was fitted into the frame under the button so that the proximal end would press against the terminal attached to the frame, so that the box and the frame could be attached to the

when the distal end was pushed up. A bolt,  $1\frac{1}{2}$  inches long, was fitted into the distal end of the lever. The head of the bolt was one-half inch wide and made slightly concave, so that it was more adaptable for fitting against a tendon or muscle. The head of the bolt is the part of the myokinesiometer which receives the force of the muscle during contraction.

A slight pressure upward against the lever causes the lever to press against the bottom terminal. Variations in pressure against this button change the amount of current flowing through the button. The button with its frame is attached to the thigh by elastic bands. The elasticity of the bands is sufficient to prevent the influence of other muscles in the thigh (fig. 1).

By means of an electric wire, 25 feet (7.62 meters) in length, the myokinesiometer was attached to a polygraph. The magnetic field about the coil fluctuates in accordance with the variation of the current from the myokinesiometer. A small light steel rod was suspended in front of the coil. As the magnetic field

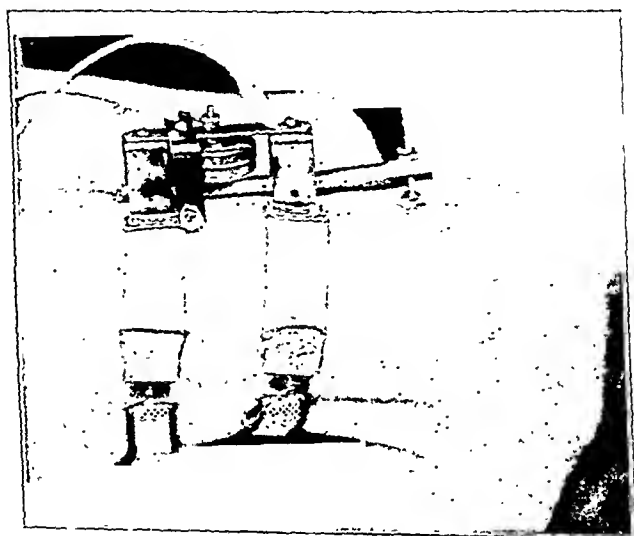


Fig. 1.—Myokinesiometer.

changes in intensity, the magnetic force is correspondingly altered. The steel rod is attracted according to the strength of the magnetic field. The greater the action of the muscle, the greater is the excursion of the rod. The steel rod was in turn connected to a recording pen on the polygraph. Three dry cells provide the electric current for the myokinesiometer and the recording device.

In this study I have used a procedure similar to the one used by Scherb in comparing muscular action with certain phases of gait. Scherb divided gait into two main phases: (1) the phase of double support or the period during which the subject stands on both feet and (2) the swinging phases, or the period during which the subject stands on one foot and swings the other. In normal gait, the following order occurs: (1) double support, (2) swing (left or right), (3) double support and (4) swing (right or left). A muscle usually acts during more than one phase. The period of double support is only momentary in ordinary



gait, and it is difficult without mechanical aid to observe just when these phases begin and end. For this purpose a Scherb sandal, with modifications necessary for the recording of the contractions, was constructed, as follows:

In the sole of the sandal I inserted two flat switches, one in the inside and the other in the outside of the sole. A third switch was inserted in the heel. The switch consisted of two pieces of tin  $1\frac{1}{2}$  inches square separated by thin rubber sheeting, care having been taken that the edges of the switch did not come in contact with each other. In the center of the switch a piece of rubber about one-half inch square was removed. This made it possible to close the switch by exerting a small amount of pressure over the switch, thereby bringing the two pieces of tin into close contact. When the pressure is removed the contact is broken. A signal magnet was provided for each separate switch. The switches were attached to the signal magnet by 25 feet of wire. This length of wire makes it possible for



Fig. 2.—Sandal with electric switches in the sole.

the subject to walk without danger of pulling the polygraph, with its attachments, from the table (fig. 2). Each signal magnet records the time the heel, the outer side of the sole and the inner side of the sole come in contact with the floor. The current from two dry cells operates the switches and the signal magnet.

By obtaining these records it is possible to determine the various phases of gait. If the sandal is worn on the right foot, the beginning of the right swinging phase is marked when the switch on the inner aspect of the sole is released. The end of the right swinging phase is recorded by the closing of the heel switch. The two double support periods and the left swinging phase occur between the right swinging phases. The periods of double support are only momentary and are not especially significant (fig. 3).

By the use of this instrument and method it is possible to record accurately the contractions of the muscles. I examined fifteen persons

with normal gait and compared my results with those of Scherb. It is obvious that it is impossible to examine all of the muscles, as they are covered by other structures such as the psoas, popliteus and small rotatory muscles of the hip. Only a few muscles remain active throughout the swinging phases. The sartorius is active throughout the entire swinging phase and from the time the heel touches the ground to the time all three points have touched. In the swinging motion the sartorius is an



Fig. 3.—Complete set-up of apparatus.

extensor, and in the support period it maintains extension but also holds itself in readiness as an external rotator as the heel touches the ground.

The curve of the gastrocnemius corresponds with the muscles of the thigh. It goes into action when the knee is flexed and when the heel begins to leave the floor.

All of these facts are shown on the myokinesiogram. Deficient muscles can be demonstrated by this procedure, and, of utmost importance, actual antagonists can be determined. The use of an antagonist muscle is always a doubtful procedure because of the difficulty of rear-

ranging impulses from the central nervous system. In order to decide on a transplantation procedure to replace a paralyzed muscle or to re-enforce a weak or partially paralyzed muscle, one must determine the nature of the muscle to be transplanted. The myokinesiometer will be a great factor in the proper selection of the muscle for transplantation. With its use, accurate information regarding muscular action can be determined without undue influence of the examiner's judgment.

I shall first discuss a series of records of normal action of the muscles about the knee. The subjects chosen had no impairment in gait, and their muscular action was considered normal. A treadmill like the one Scherb used for his examinations was found to be a factor in producing abnormal gait; therefore it was successfully eliminated in this study. It was observed that subjects were afraid that they would fall from the treadmill when unsupported. A more serious objection to the treadmill was that the rate of gait was not determined by the patient but by the speed of the treadmill. The subjects in this series walked at their normal rate of speed. This was regarded as essential in the proper analysis of normal gait. The myokinesiometer was used in the study of all of these cases. The graphs obtained are shown in figures 4 to 10. Only the muscles about the right knee were examined. Figure 4 is a record of the normal biceps femoris; figure 5, of the normal inner hamstrings, and figure 6, of the normal quadriceps.

The three phases of gait were determined on the graphs. Since only one special sandal was used, it was possible to show definitely one phase of gait—the right swing. The other phases were mathematically determined. The period of right swing is shown on the graph by the space from the point where the switch under the inner side of the foot is released (line *C* on the graph) to the point where the switch in the heel is closed (line *B*). The making and breaking of the various switches in the shoe are indicated by notches in the respective lines on the graph. The line made by the heel switch extends in an opposite direction to that of the other two lines.

The periods between the phases of the right swing necessarily consist of two periods of double support and one of left swing. It is reasonable to assume that the period of the left swing is approximately of the same length as that of the right swing; therefore it covers about the same distance on the graph. If this distance (the length of the right swing) is measured in the space between the right swinging phases, the remaining distance is the length of the two periods of double support. Since there are two double supporting periods, the distance is divided by two, and the actual length of each double supporting period is known. These various periods have been designated on the graphs by vertical lines in the appropriate places.

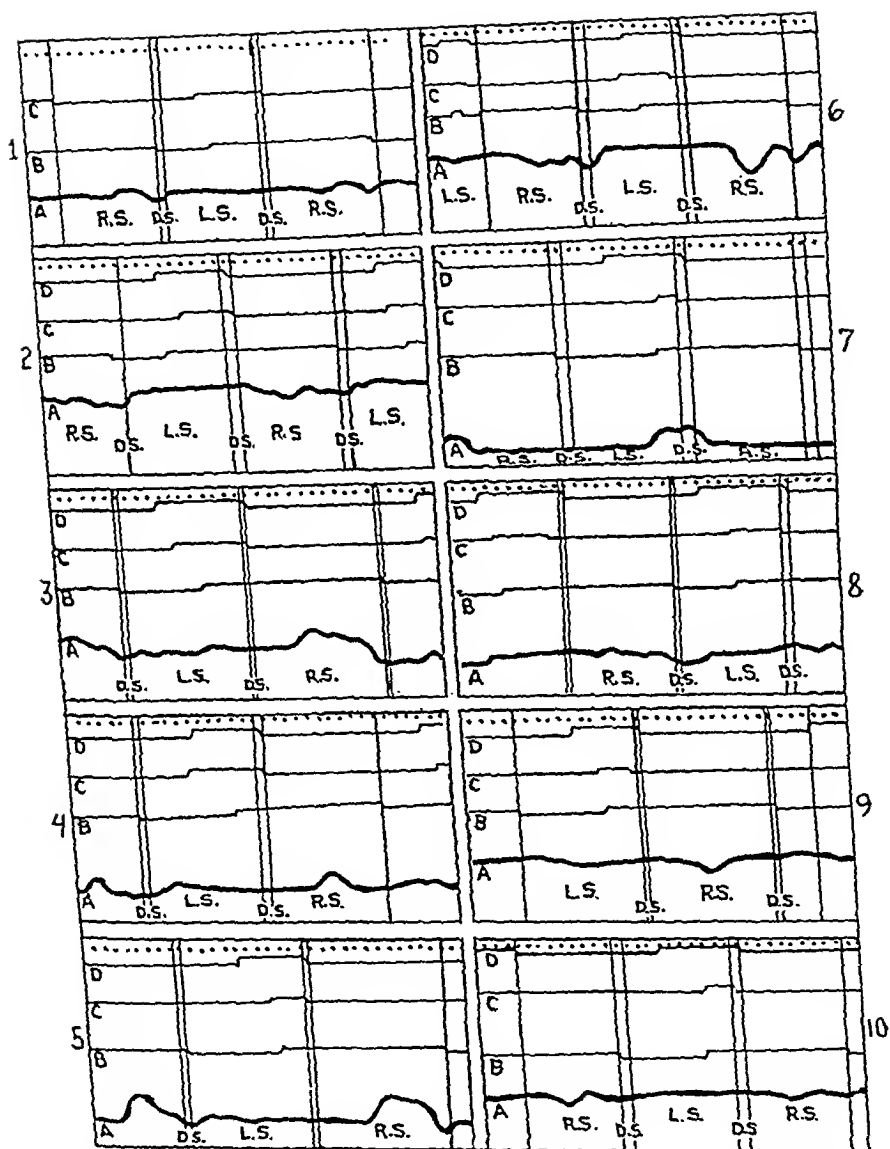


Fig. 4.—Myokinesiograms of normal biceps femoris: A, line showing the muscle contraction; B, line showing the time when the right heel is bearing weight; C, line showing the time when the forward outside portion of the foot is bearing weight, and D, line showing the time when the forward inside portion of the foot is bearing weight. In this and the remaining charts D.S. indicates double support; R.S., the right swing, and L.S., the left swing. The dotted line indicates the time interval; each space denotes one-tenth second.

The subjects in these examinations walked at a normal rate of speed. The period of double support is short in normal gait. In this series of cases it varied from 0.02 to 0.12 second. In Scherb's examinations

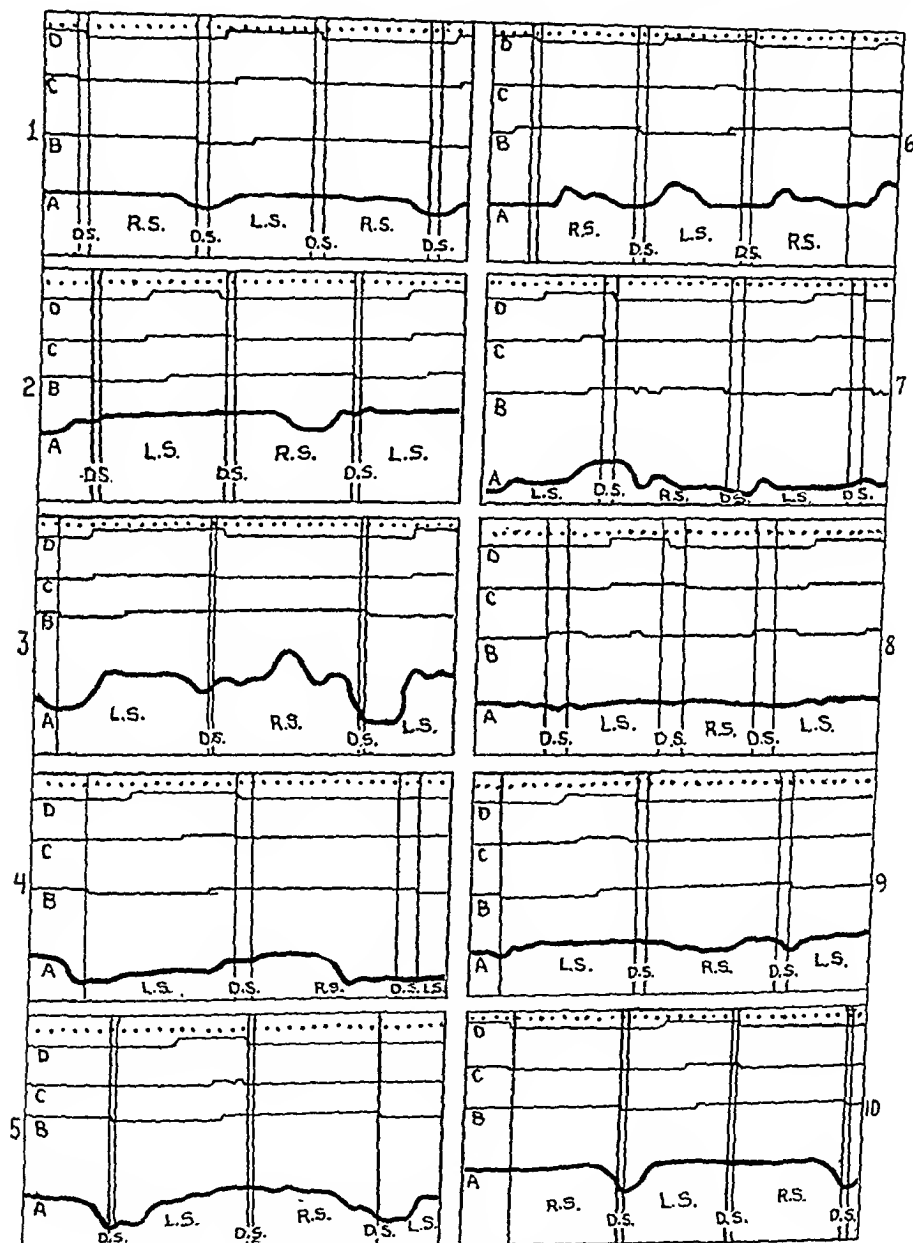


Fig. 5.—Myokinesiograms of the inner hamstrings.

the period of double support necessarily had to be longer, because his patients walked slowly in order that he might palpate properly; consequently the action in normal gait was unobtainable. There is a great deal of individual variation in muscular action, as shown by the myokinesiograms.

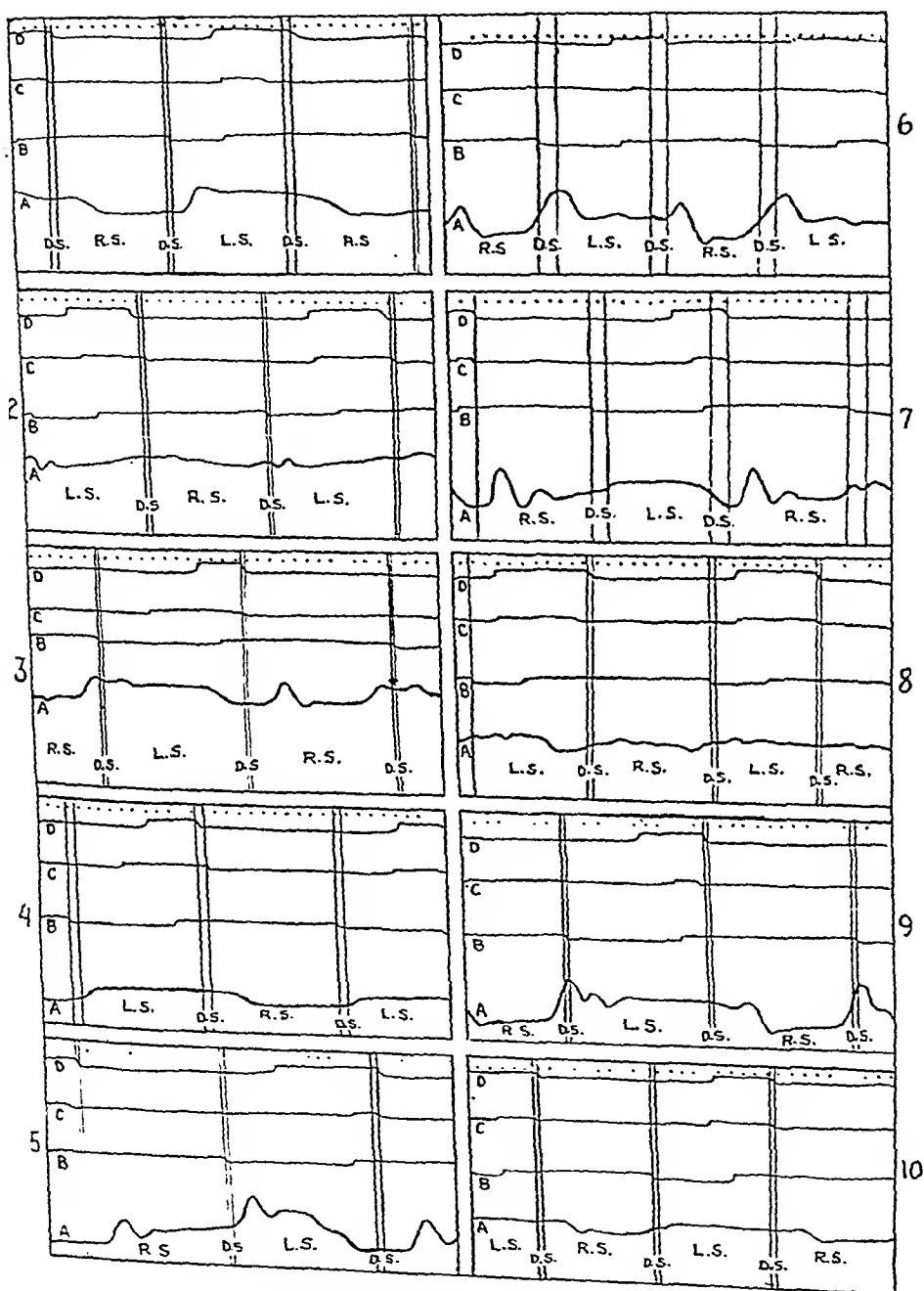


Fig. 6.—Myokinesigrams of the normal quadriceps.

In spite of the enormous individual variation, certain features characterize the individual muscles. It was found to be feasible to examine the quadriceps muscles as a group because they have a common insertion. The quadriceps relaxed during the period of right swing, and began to contract strongly during the period of double support after the right swing or during the first part of the left swing. Individual differences were shown by slight variations in the periods of contraction, as compared with certain phases of gait, and also by the intensity of the muscular action during the contraction wave. The period of time that the patient bore weight on various parts of his foot also varied considerably according to the individual and the speed of gait. The actual significance of this observation has not been determined.

Dr. J. T. McClintock suggested that the hamstrings might affect the record of contractions because the elastic band was fastened completely around the thigh. In order to evaluate this, I strapped the myokinesiometer to the thigh with adhesive tape. This resulted in no difference in the record. The elasticity of the bands around the thigh was sufficient to rule out the possible influence of the hamstrings.

The findings recorded by the myokinesiometer do not show the regular smooth contraction which Scherb determined by palpation but individual variations in intensity and time of action.

Examination of the gracilis, semimembranosus and semitendinosus gave results corresponding with the findings of Scherb, but individual variations were again marked. Graphs 3 and 8 in figure 5 show the extremes in individual contractions. The period of the muscular contractions usually began during the first part of the left swing and continued through the periods of left swing, double support and right swing. The period of relaxation began near the end of the right swing and was completed during the period of double support following the right swing. It was evident that the period of contraction of these muscles is extremely long.

Graph 8, figure 5, shows a weak contraction. This particular subject had poor musculature, and consequently, little contraction is noted on the graph. The inner hamstrings acted as inward rotators of the knee joint, as well as flexors; under certain unusual conditions these muscles act as extensors.

The biceps relaxed only during the period of double support following the right swing in the majority of the cases observed. However, in a few cases relaxation occurred during the right swing. This follows Scherb's observations closely. The contraction acts over a long period of time, and is similar to that of the inner hamstrings in that it begins during the period of the left swing and continues through the period of double support and the right swing. It relaxes near the end of the right swing.

The hamstrings are synergists and in relation to certain phases of gait are similar in action. It is obvious that as far as muscular action alone is concerned, they could be interchanged by transplantation. The fact that the hamstrings can act as extensors under certain conditions and have a long period of contraction at the same time that the quadriceps muscles contract makes them suitable for transplantation to the quadriceps in cases of insufficiency of the extensor.

The foregoing records were taken in series and are not from selected cases. They represent a few of the variations that occur. Undoubtedly, if a large series of cases were examined, many interesting variations would be shown. What influence these variations have on normal gait and in transplantation of tendons can be determined only by careful study before and after transplantation.

Individual characteristics of muscular contraction can be determined only by delicate mechanical means and not by direct palpation, the method used by Scherb. These characteristics of muscular contractions are shown by the use of the myokinesiometer. A certain amount of care and technic must be used to obtain accuracy. The contact plate of the myokinesiometer must be placed directly over the muscle tendon. Furthermore, the plate must be adjusted so that with proper tension the slightest movement of the lever causes a motion of the recording pen.

A few patients who had had transplantations of tendons about the knee were examined in this manner with the myokinesiometer. One object of these examinations was to determine whether the transplanted muscle retained its original action in relation to gait or if it acquired the action of the muscle it replaced, thus the advisability of replacing a muscle by its antagonist. The records of cases of transplanted muscles are shown in figures 7 to 10.

In case 1 (figure 7) the right biceps femoris was transplanted to the quadriceps tendon. The insufficiency of the quadriceps was due to infantile paralysis. The biceps was unaffected by the disease. The action of the biceps was similar to its action in the normal position. The quadriceps worked strongly with the aid of this muscle. The inner hamstrings continued to act in their usual manner in spite of the fact that their synergist was transplanted. The patient also had considerable paralysis of the left leg, necessitating the use of a long brace. The patient walked with a marked limp, causing his gait to be slow, and therefore the period of double support was long. The period of right swing was about twice as long as that determined in normal gait. The top dotted line on the graph denotes the interval of time, each space denoting six-hundredths second, so that each swing lasted about 1.2 seconds. In spite of the slow, abnormal gait, the muscles retained a normal action in relation to gait. Although this patient still had a pathologic gait, the transplantation of the biceps caused marked improvement.



Case 2 (figure 8) was also one of infantile paralysis involving the quadriceps. The right tensor fasciae was transplanted to the weakened quadriceps. The transplanted muscle evidently aided little, if at all, for the action of the quadriceps continued to be weak. This patient had considerable shortening of the involved extremity. His gait was necessarily awkward. He compensated for his insufficient quadriceps action by swinging his entire lower extremity forward. The action of the

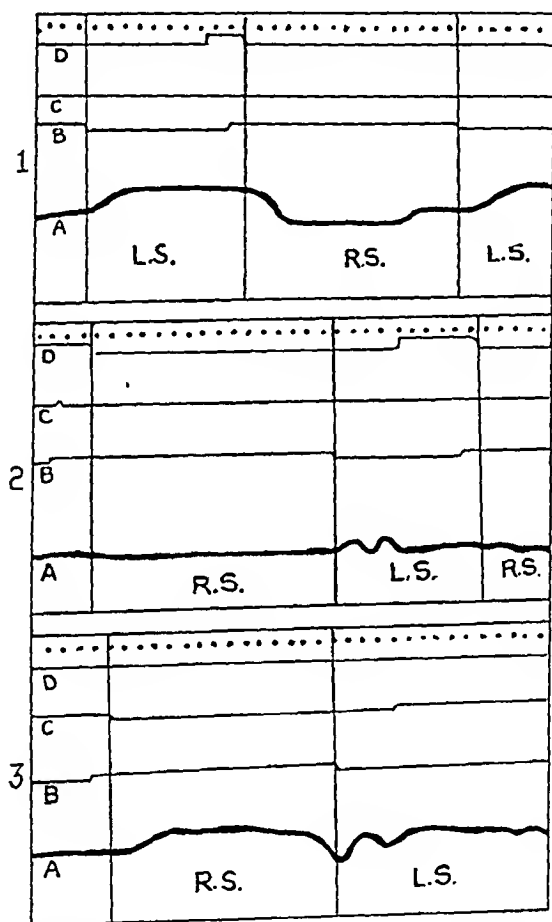


Fig. 7.—Myokinesigrams of the (1) biceps, (2) quadriceps and (3) the inner hamstrings following transplantation of the biceps transplanted to the quadriceps.

biceps femoris was abnormal in that a long period of relaxation occurred during the right swing. This apparently was a mechanism to facilitate the extension of the knee, showing that it can be changed under certain mechanical situations with the main characteristics of the muscular contraction wave remaining intact. It is, however, peculiar and perhaps contradictory to the foregoing statement that the inner hamstrings did not show a similar period of relaxation. The period of double support was not determined in this case, because the patient walked with a

smaller step on the right than he did on the left. In a case of this sort a sandal on each foot would be necessary to determine accurately the double supporting period. Transplantation of the tensor fasciae has been practically discontinued. This patient would have received more benefit, I believe, from a transplanted biceps femoris.

Case 3 (figure 9) was one of spastic hemiplegia. The right biceps femoris was transplanted to the insufficient quadriceps. Graph *A* shows

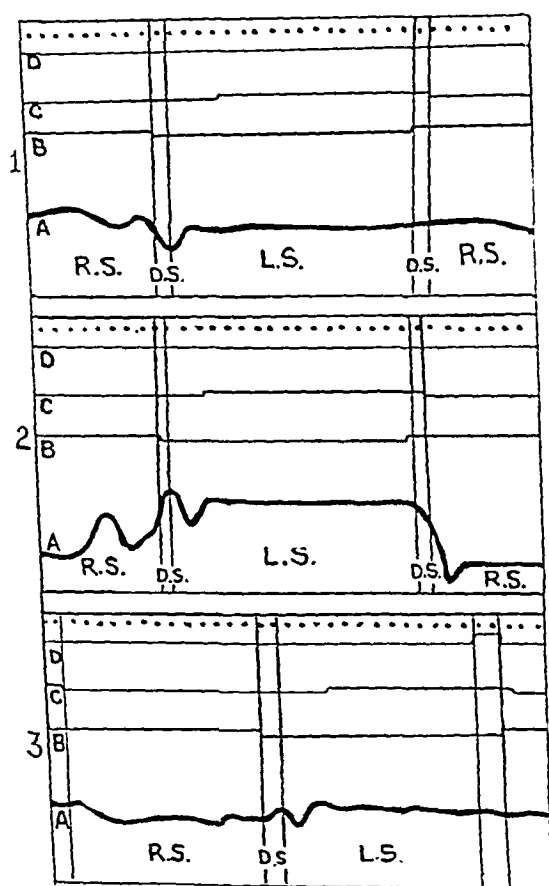


Fig. 8.—Myokinesigrams of the (1) biceps femoris, (2) quadriceps and (3) inner hamstrings following transplantation of the tensor fasciae to the quadriceps.

a relaxation between the right swing and the left swing, with a sharp contraction at the beginning of the left swing and no relaxation between the left swing and the right swing, including the period of double support. It is evident that a dissociation of muscular function did not occur. This, however, does not contraindicate transplantation, for the patient's gait was decidedly improved. The quadriceps action was strong. It is a matter of conjecture whether or not the small elevation

in the center of the quadriceps wave was due to the action of the biceps contraction, especially since it occurred at almost the same time that the biceps made a violent contraction. The inner hamstring showed a marked relaxation between the right swing and the left swing. This contraction wave was similar to that of the normal inner hamstring in case 3. The spasticity apparently did not make itself evident in the contraction wave.

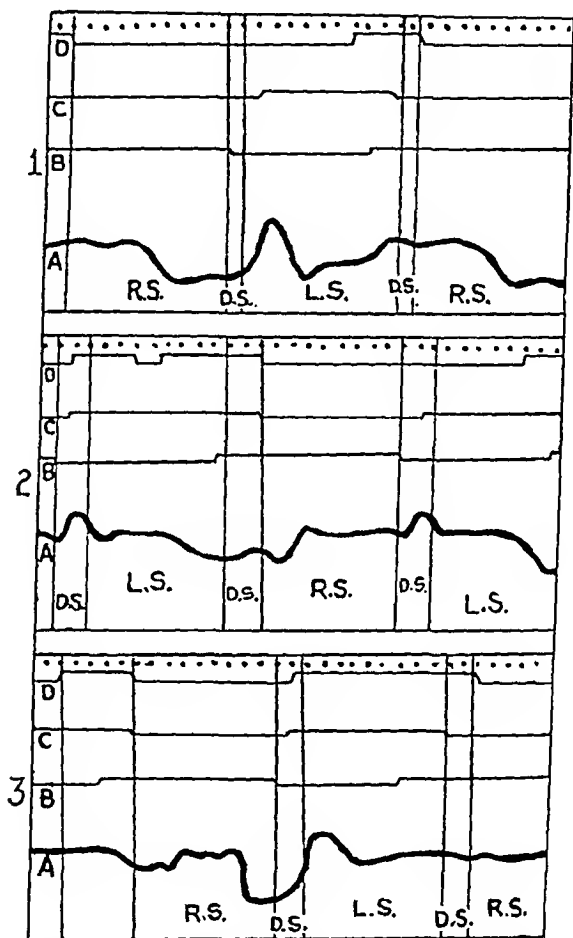


Fig. 9.—Myokinesiograms of the (1) biceps, (2) quadriceps and (3) inner hamstrings, following transplantation of the biceps femoris to the quadriceps.

Case 4 (figure 10) was another instance of spastic paralysis. The left biceps femoris was transplanted to the quadriceps. The biceps again showed the usual contraction wave, and this fact further supports the contention that dissociation does not take place. The quadriceps showed a rather weak contraction wave in spite of the fact that it was aided by a transplanted muscle. The patient felt certain that the operation had markedly improved her gait. The inner hamstrings had a more or less

normal action. The patient walked with both legs inwardly rotated and with slight flexion of the hip joints.

It is unfortunate that more patients were not available for examination in this study. In view of the small number of cases, sweeping conclusions cannot be made. Nevertheless, evidence has been obtained that the transplanted muscles retain their original or nearly their original contraction wave after transplantation. These factors are of importance

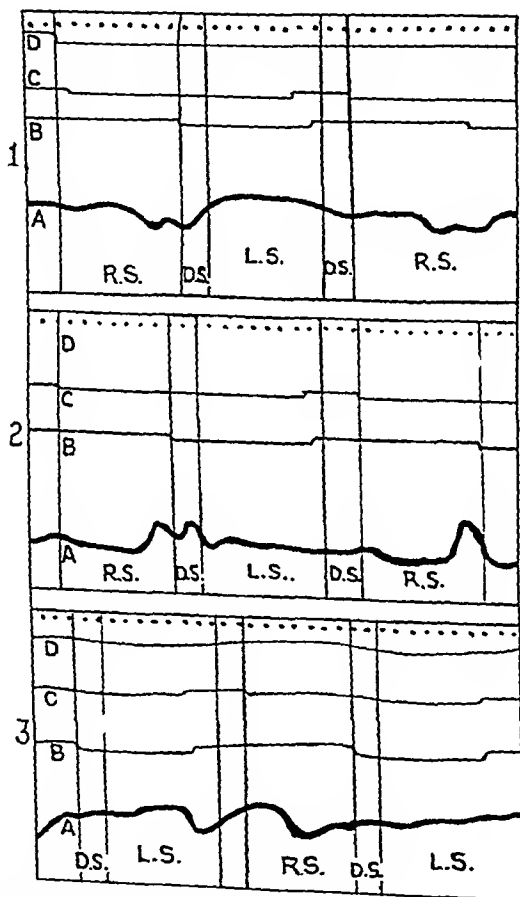


Fig. 10.—Myokinesigrams of the (1) biceps femoris, (2) quadriceps, and (3) inner hamstrings following transplantation of the biceps femoris to the quadriceps.

in transplantation of tendons and muscles, for it is obvious that if a muscle retains its original action in relation to certain phases of gait, it will be the muscle of choice for the replacement of a similarly acting insufficient or paralyzed muscle. The study of transplantation of muscles in both spastic and infantile paralysis shows that the biceps femoris can be transplanted to the quadriceps with good clinical results. Normally, the biceps femoris contracts during the left swing at the same time that the quadriceps acts; therefore, when the biceps femoris is

transplanted, it definitely aids the action of the quadriceps, in spite of the fact that its original action continues.

Isometric contractions make themselves evident in the records obtained by the use of the pill-box myokinesiometer, although from a purely theoretical basis this is not possible. In isometric contractions, a certain amount of slack and elasticity must be absorbed before the tendon is taut. When the tendon changes from a relaxed to a taut condition, or vice versa, enough motion takes place in the muscle or tendon to make a record on the graph.

#### CONCLUSION

A new instrument, the myokinesiometer, for the study of muscular function, has been described. In conjunction with this device, a sandal with special electrical switches was constructed to determine various phases of gait. The method outlined is useful in making the proper selection of muscles for transplantation. Myokinesigrams obtained by the use of this apparatus show a variation in muscular contractions. Other points of academic interest can likewise be determined by the use of the myokinesiometer.

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# INTUSSUSCEPTION IN INFANCY AND CHILDHOOD

A REPORT OF THREE HUNDRED AND SEVENTY-TWO CASES

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During the twenty-five year period from 1908 to 1932, inclusive, 121,515 patients were admitted to the wards and private wing of the Children's Hospital, Boston, and in this time 372 cases of intussusception were encountered. This report is based on a study of these 372 cases. In order to show the improvement in treatment of intussusception, analyses have been made for the first twenty year period, from 1908 to 1927, as contrasted with the last five year period, from 1928 to 1932. References were made to 63 of these cases in 1915 (Ladd) and to an additional 99 in 1925 (Ladd and Cutler).

## INCIDENCE ACCORDING TO AGE AND SEX

Eighty-seven per cent of the cases occurred in children under 2 years of age, and 70 per cent in children between the ages of 4 and 11 months, with the peak of incidence in those at 7 months. The youngest patient was 17 days old, and the oldest of the series was aged 11 years. Table 1

TABLE 1.—Incidence According to Age (372 Cases)

Age	Cases	Age	Cases	Age	Cases	Age	Cases
1 month.....	1	10 months.....	23	19 months.....	5	4 to 5 years...	11
2 months.....	8	11 months.....	16	20 months.....	3	5 to 6 years...	5
3 months.....	10	12 months.....	4	21 months.....	2	6 to 7 years...	3
4 months.....	27	13 months.....	8	22 months.....	3	7 to 8 years...	2
5 months.....	44	14 months.....	3	23 months.....	1	8 to 9 years...	2
6 months.....	46	15 months.....	2	24 months.....	3	9 to 10 years...	1
7 months.....	50	16 months.....	3	2 to 3 years....	12	10 to 11 years...	1
8 months.....	32	17 months.....	2	3 to 4 years....	11	11 to 12 years...	0
9 months.....	25	18 months.....	3				

shows the distribution of the cases in age groups, and figure 1 graphically illustrates these statistics. Figure 2 shows the distribution of cases in the group under 18 months of age. The condition was found to be more common in boys than in girls, the proportion being 226 boys (61 per cent) to 146 girls (39 per cent).

From the surgical service of the Children's Hospital.

## PATHOGENESIS

Unfortunately, from the study of our material, no contribution has been made to the knowledge of the pathogenesis of intussusception. Some of the invaginations were caused by inverted Meckel's diverticula (14 cases), intestinal polyps (2 cases), enterocyst (1 case), lymphoma

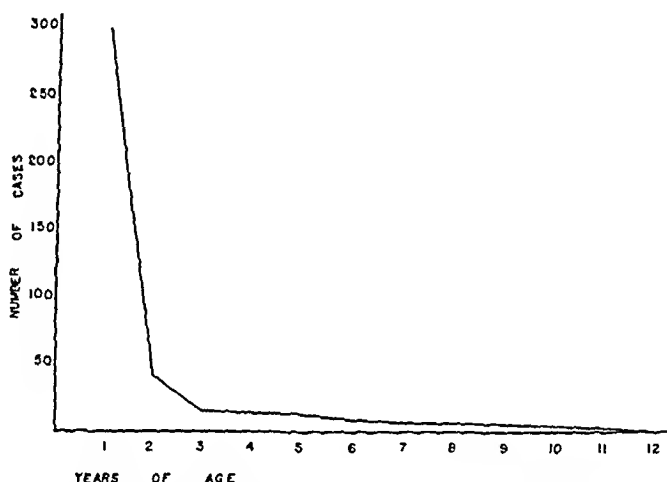


Fig. 1.—The distribution of 372 cases according to age.

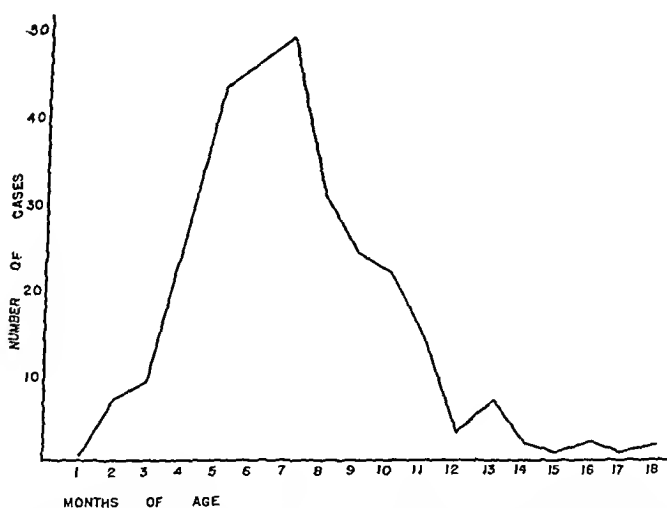


Fig. 2.—The distribution of 307 cases according to age in the group under 18 months old.

of the ileum (1 case) or other lesions of the bowel. Yet these cases comprised only 5 per cent of the series. This leaves a large group in which there was failure to detect the causal factor.

Fraser mentioned that intussusception is commonest among children of the poor because errors in diet are most frequent in this class. Our

studies do not support his contention, for the incidence in patients who entered the private wing was approximately the same as in those who entered the public wards. In addition, the condition occurred most frequently in well developed and well nourished infants—obviously not those in whom dietary errors were common.

Several tabulations appear in the literature which show a slightly higher incidence in December and in either April or May, presumably because festivities around Christmas and Easter lead to dietary indiscretions. However, no appreciable increase during these seasons was found in our series.

No familial tendency was noted, for in only two families was there a second case of intussusception.

TABLE 2.—Types of Intussusception in 372 Cases

Type of Intussusception	Cases, per Cent
Ileo-ileal (enteric).....	7
Ileocolic.....	15
Ileo-ileocolic.....	9
Colocolic.....	2
Type not stated.....	1
Multiple intussusception.....	(3 cases)
Retrograde intussusception.....	(1 case)

TABLE 3.—Points of Origin of Intussusception in 372 Cases

Leading Point	Cases	
	Number	Percentage
Ileum—above the distal 1 foot.....	60	16
Terminal ileum, ileocecal valve and cecum.....	274	74
Ascending colon.....	6	1.6
Hepatic flexure.....	5	1.3
Leading point not stated.....	27	0.7

In 7 cases, intussusception occurred as a sequel to dysentery or infectious diarrhea.

#### TYPES OF INTUSSUSCEPTION

Intussusceptions were listed as ileo-ileal (enteric), ileocolic (fig. 3), ileo-ileocolic and colocolic, depending on the point of origin and the position to which the intussusceptum had progressed.<sup>1</sup> The ileo-ileocolic form is that in which the ileum telescopes into itself first, after which the terminal portion of the ileum passes into the colon from a second leading point. A retrograde intussusception is said to occur only at the time of death or impending death, but we have had 1 case of ileal retrograde intussusception with recovery. Table 2 shows the

1. The intussusceptum is the invaginated portion, and the intussusciens is that part which receives the intussusceptum.



frequency of occurrence of the various forms and table 3 the points of origin.

#### SYMPTOMS

In this series of cases of acute intussusception the onset of symptoms was characteristically sudden, and the mother could usually tell the exact time at which the child was taken sick. In a typical case, the infant while in excellent health suddenly cried out in extreme pain,

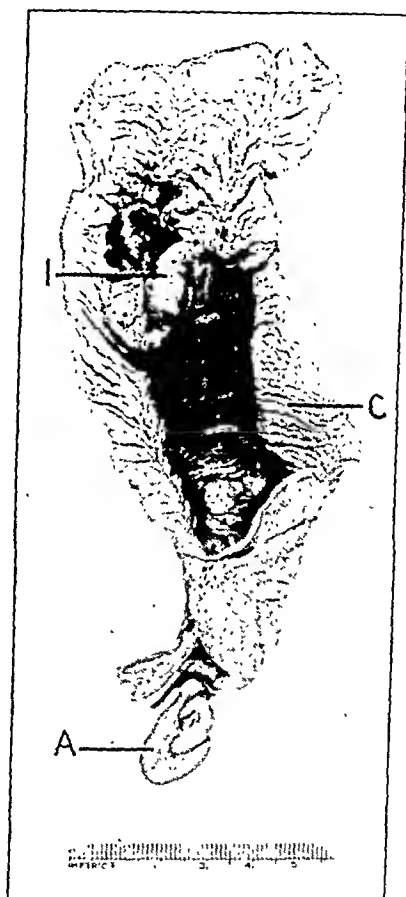


Fig. 3.—A specimen of the common type of ileocolic intussusception, showing the ileum telescoped into the ascending colon: *A*, appendix; *C*, ascending colon; *I*, intussusceptum (ileum).

“doubled up,” turned pale, sweated and vomited soon afterward. Such a paroxysm lasted for a minute or two, and was followed by a period of relief. The attacks recurred at intervals of from ten to fifteen minutes. Between attacks the child went to sleep or was playful and without complaint. In 82 per cent of the cases in this series there was a manifestation of pain, in 90 per cent there was vomiting, and in a high percentage there were sweating and pallor. Fever, however, was a less

common symptom, and its presence was indicative of long-continued vomiting and dehydration.

Blood appeared in the stools in 88 per cent of the cases within twenty-four hours after the onset of symptoms. The first stool after the beginning of the illness was often normal, since it represented an evacuation of material that previously had filled the rectum. Later stools contained mucus, mucus and blood or unmixed blood.

The history usually suggested the correct diagnosis. However, when the child was seen in the early stages and between the paroxysms of pain and vomiting, his healthy appearance tended to make one disregard the story of the parent. Hence it was found that the history was very important whether or not the child looked sick.

In the chronic and subacute forms of intussusception, pain was a less prominent feature, but was usually the chief complaint. Blood was often absent from the stools. Because of infrequent vomiting, dehydration was slight or absent. While the symptoms were of relatively long standing, their mildness was demonstrated by the fact that the patients often continued in fairly good health.

#### PHYSICAL FINDINGS

One of the most characteristic findings of intussusception in this study was its frequent occurrence in a well nourished and well developed child. However, by the time the patient was seen in the hospital, he was pale and listless though in a good state of nutrition. When vomiting was of long standing, dehydration was present. In about one tenth of the cases the condition of shock was marked. Twenty patients were classified as moribund on entry and were in such extremity that 9 died before operation could be performed, and 4 others died during the course of immediate laparotomy.

In 312 cases (84 per cent of the series) abdominal examination revealed the presence of a mass. This was poorly defined in some instances, but was usually a discrete, rounded or sausage-shaped tumor. The mass was rather firm and was not tender (tender in only 6 instances). Occasionally it was felt to increase in hardness during the attacks of pain. Since the great majority of the intestinal invaginations had proceeded into the colon the mass was found along the course of that organ. When the intussusceptum was in the hepatic flexure, it was sometimes difficult to detect because of the overlying liver. Palpation of the mass in the epigastrium or on the left side of the abdomen, indicating an advanced intussusception, was at times accompanied by an "empty" right lower quadrant of the abdomen (Dance's sign) because of the invagination of the cecum up into the colon.

When the history was suggestive of intussusception and when abdominal examination was unsatisfactory because of distention or because the child was fretful and uncooperative, we made it a rule to make an immediate examination under ether anesthesia. Before the examination was made, however, all preparations were completed for an immediate laparotomy. In 10 cases the tumor was felt only after the patient was thus anesthetized.

The palpation of the intussusceptum within the rectal lumen in 106 cases (28 per cent of the series) showed the value and importance of rectal examination. When felt with the examining finger, the advancing portion of the bowel had the general shape of an adult cervix uteri. Even though the tip of the advancing mass was not always encountered in the rectum, bimanual examination occasionally revealed a tumor higher up in the peritoneal cavity, which would have eluded detection by abdominal palpation alone. Shelley recommended bimanual palpation with the baby held in a sitting posture, because the tumor will then usually drop down between the examiner's fingers. In 4 cases the intussusceptum had proceeded so far that it protruded from the anus; in 2 of these cases the children were referred for "treatment of prolapsed rectum." The differentiation between intussusception and prolapsed rectum could be made rapidly by passing the finger into the rectum between the intussusceptum and the surrounding anal sphincter. In prolapse of the rectum there is no such space to admit a finger.

After withdrawal of the examining finger blood was detected in 183 cases (50 per cent). In 11 of these no suggestion of rectal bleeding had been noted in the history. The blood appeared to be undiluted, intermingled with mucus or admixed with feces. Often it was described as appearing similar to prune juice.

Fever was absent in patients brought to the hospital soon after the appearance of symptoms, but was present in those who had had symptoms long enough to become dehydrated.

#### ROENTGENOGRAPHIC OBSERVATIONS

In the typical cases of acute intussusception, which formed the majority of this series, the history and physical findings led to a positive diagnosis and made roentgenographic studies unnecessary. There were, however, a minority of cases in which the symptoms or signs were atypical leaving the diagnosis doubtful. In this group an enema of barium sulphate, with fluoroscopic and roentgenographic studies, was a valuable aid. In 17 such instances 16 positive diagnoses were made by roentgenograms and confirmed by immediate laparotomy; in 1 case (ileo-ileal type) the roentgenographic findings were normal, but an intussusception was found at operation.

The main, typical observations made at roentgen examination following a barium enema in ileocolic intussusception were: (1) obstruction to the injection of barium; (2) a cupola effect or cupping in the head of the barium as it met the intussusceptum; (3) a thin cylindric shell of barium around the intussusceptum (and inside the intussusciens); (4) possibly a palpable tumor at the site of obstruction, and (5) a remaining cylindric shell of barium surrounding and outlining the intussusceptum after evacuation of the enema.

Lehmann, in 1913, reported the first observations on detection of an intussusception by barium enema and roentgenogram, while Ashbury,



Fig. 4.—Roentgenograms made after the administration of a barium enema. In the film on the left, a filling defect is shown in the right half of the transverse colon. In the film on the right, taken after evacuation, the barium is shown remaining around and outlining the intussusceptum in the hepatic flexure and the right half of the transverse part of the colon. The accumulations of gas in the right flank are indicative of intestinal obstruction.

Stephens, Sussman and others treated this subject more fully in their respective articles.

#### TREATMENT

In 1874 Hutchinson performed the first abdominal section with successful reduction of an intussusception, and since that time the treatment of this condition has tended toward operative intervention. In spite of the almost universal adoption of surgical treatment, there have been

several published reports, notably those of Hipsley, Kock and Oerum and Mourad, which favored the method of reduction by colonic injection of fluids. Arntzen and Helsted, Retan and Stephens advocated reduction by the injection of a barium enema under fluoroscopic observation. We are opposed to all such methods of reduction by colonic inflation. In those clinics in which this type of treatment is employed, a considerable number of the cases come to operation because of irreducibility or to make certain that complete reduction has been effected. Operation is therefore necessarily delayed, and the child is subjected to a procedure which depletes its narrow margin of reserve. By limiting ourselves to operative treatment a simplification resulted which appreciably aided in reducing the mortality.

Various surgeons have employed the following types of operations: (1) reduction; (2) resection with anastomosis; (3) resection with double enterostomy (Mikulicz); (4) removal of intussusceptum through incision in intussusciens (method of Coffey, Maunsell or Jessett); (5) anastomosis around the mass, leaving the intussusceptum to slough out; (6) anastomosis around the mass and resection of the intussusceptum at a second operation, and (7) ileostomy, with resection at a second operation.

Our series included examples of each of these except the last two.

Since intussusception has been regarded as an urgent surgical emergency it has been our practice to perform laparotomy immediately. The average patient was admitted, operated on and put to bed within from forty to fifty minutes. When dehydration was marked, parenteral fluids were given before operation. The time required to admit, give dextrose intravenously and saline solution subcutaneously, and be ready for operation was rarely more than thirty minutes.

The anesthetic used in all cases was ether. In some of the earlier operations an incision in the midline of the lower part of the abdomen was made, but since then a right paramedian rectus incision has been commonly employed, because the most difficult part of the reduction occurred in the region of the cecum or lower part of the ileum. Hence the incision was not made over the palpable tumor unless the mass happened to be in the right lower quadrant of the abdomen.

As far as possible reduction was performed intra-abdominally. This was done by a process of milking back, or "taxi," by putting gentle pressure over the intussusciens with the hand and squeezing out the invaginated part. Unfortunate experience has shown that the intussusceptum should never be pulled out, for if the intestine is friable, a rupture and peritoneal soiling result. In the region of the cecum and ileum the reduction often became difficult or impossible, and at this stage the mass would be delivered outside the abdomen. Continued

annular pressure with the hand and a stretching of the receiving ring usually reduced the edema enough to allow complete reduction. Application of hot isotonic saline solution during the manipulation aided the reduction. An intestine that looked bluish, discolored and of questionable viability often improved in a few minutes.

In recent years attempts at reduction have been persisted in more than formerly, for continuance of this procedure was often successful, whereas early recourse to resection would undoubtedly have resulted in more fatalities. Not infrequently the serosa was accidentally split as much as 6 inches (15 cm.), but this did not prove to be a serious complication. A few quickly placed stitches of silk or fine catgut sufficed to bring the serosal edges together. Brown suggested deliberate incision of the serosa to permit reduction.

Reduction was effected in 308 cases (83 per cent), with a mortality of 27 per cent in the first twenty year period as compared with 12 per cent in the last five years. In conjunction with reduction the following procedures were done as indicated: 1. The ileum was drained in 9 cases when the intestine was of doubtful viability. In 2 of these, this was accomplished by opening a Meckel diverticulum. 2. In 7 other cases a Meckel diverticulum was excised. 3. In 13 cases the appendix was removed. 4. In 1 case the terminal part of the ileum was sutured down to the parietal part of the peritoneum in an attempt to prevent recurrence.

An appendectomy was performed twelve times during the first twenty year period, but only once during the last five years, for we have come to believe that nothing more should be done than is absolutely necessary. While removal of the appendix requires only a few minutes, it is an additional trauma which may lead to death in children who are extremely ill. Involvement of the appendix in the intussusception makes it reddened and swollen, but this condition must not be confused with appendicitis. Various authors have reported that they removed the appendix as a routine, believing that irritation from appendicitis induced the spasm which brought about the invagination. We place little credence in this view and do not believe that the appendix should be removed unless it is gangrenous or its vessels are thrombosed.

In babies under 1 year of age resection of intussusception has carried a high mortality. In 1921 Clubbe reported 2 successful resections and collected 17 instances from the literature. He did not include the reports of Eisendrath and of Frank—the latter being the first to perform and record a successful resection in an infant in this country. Without exhaustive search, 6 cases have been found recorded since 1921, bringing the total to at least 30. Clubbe performed the first successful resection in 1896. Robbins reported the most extensive resection, with

removal of the terminal part of the ileum, the cecum, the ascending colon, the transverse colon and a portion of the descending colon, followed by a successful ileosigmoidostomy. Dowd, in operating on a 5 day old infant, performed a successful resection in the youngest patient on record for this operation. But, as has been pointed out, reduction of the mortality lies not so much in improvement in the technic of resection as it does in obtaining cases before resection is necessary.

In our series 30 resections were done; in 16 there was an ileocolostomy, with 1 recovery, and in 14 there was a double enterostomy (Mikulicz' procedure), with 1 recovery. The 2 recoveries were in 4 year old boys, 1 with symptoms for twenty-four hours and the other

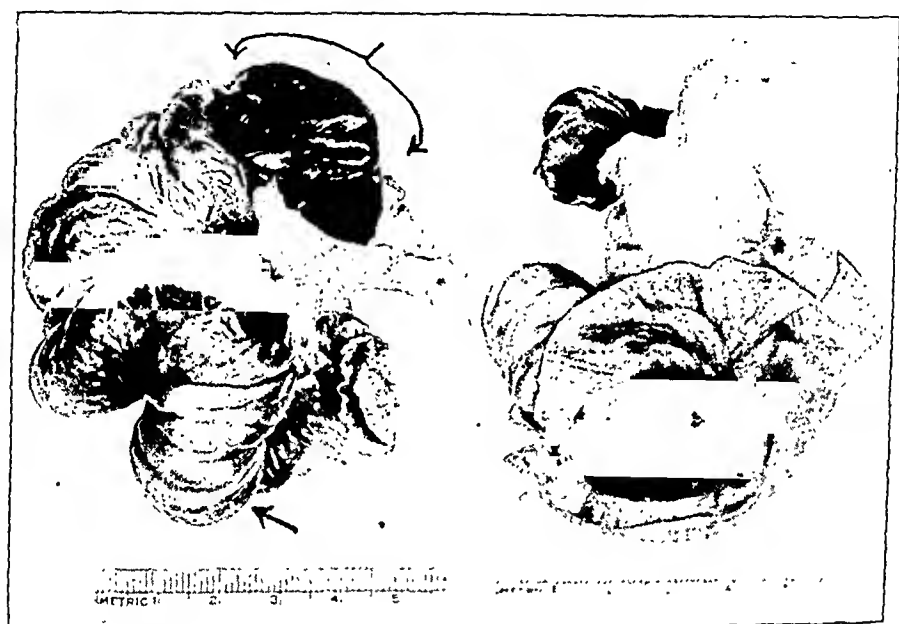


Fig. 5.—A specimen of an irreducible intussusception. In the photograph on the left the bracket at the top points out the ileum as it telescopes into the terminal part of the ileum, and the arrow at the bottom indicates the position to which the intussusceptum has advanced. The photograph on the right shows the lower portion of the ileum cut open to permit a view of the gangrenous leading point.

with symptoms for three days.<sup>2</sup> When resection was necessary, a double enterostomy was regarded as preferable to an anastomosis, though we have no figures to support the contention.

2. Since completion of this article there has been a third successful resection with establishment of a double enterostomy. This was in a 4 month old boy who had had symptoms for forty-eight hours. One of us (W. E. L.) has performed an additional successful resection at another hospital, which is not included in this series. This was in a 3 year old child, in whom a lateral anastomosis was performed.

In 3 instances of unsuccessful resection with ileocolostomy the method used was that of Jasset or of Maunsell; that is: (1) sewing the invaginating portion to the intussusciens with stitches placed around the ring or neck of entry; (2) making a longitudinal incision in the intussusciens (just distal to the line of suture), and (3) cutting off and removing the intussusceptum through this opening. The incision was used as an enterostomy in 2 cases.

In 1906 Rutherford first employed an anastomosis—ileocolostomy—around the undisturbed mass, and Parry and Bullock reported such operations in 1909 and 1920, respectively. Montgomery and Mussil, in 1930, listed two successes with this short-circuiting operation, and substantiated their work by experiments on animals. We have had experience with this procedure in only 1 case. The patient had an irreducible intussusception which originated from an intestinal lymphoma. He recovered without event, but whether or not the intussusceptum sloughed out is not known, for it was never identified in the stool. The patient was discharged with the intestinal obstruction relieved, but died three months later from a massive abdominal extension of the lymphoma.

It is important to note that there have been fewer resections in the last five years, there being only 2 in the last 90 cases (2.2 per cent) as compared with 28 in the previous 282 cases (10 per cent). This reduction was due to three factors: First, in the last five years patients were referred earlier for treatment. Second, we became somewhat more bold in attempting and completing reductions which previously would have been termed irreducible. Third, experience showed that the intestine, though badly discolored and damaged after reduction, was frequently viable, whereas formerly such an appearance would have led to resection.

Because of the high mortality resulting from reduction of an intussusception and excision of a Meckel diverticulum at the same operation (5 deaths in 7 attempts), it was better, when possible, to leave the diverticulum till a second operation so that it could be removed with more safety (no deaths in 3 cases).

In 16 cases the intussusception was found to be wholly or partially reduced at operation. In all these cases the symptoms and physical findings had been unquestionable, and in each instance there was vascular congestion with edema in the terminal part of the ileum, the cecum and the ascending colon, which was interpreted as evidence of recent intussusception. Such a finding represents either a spontaneous reduction or a reduction attendant on manipulation at examination.

The mortality in our series during the last twenty-five years has taken a continuous marked downward trend from 59 per cent in the first five years to 14 per cent in the last five years (fig. 6).



## FACTORS IN MORTALITY

The most important factor in reducing the mortality in intussusception is a reduction of the time between the onset of symptoms and the operation. This point has been demonstrated amply in other clinics and communities and too much credit cannot be given to Clubbe, Hipsley and other surgeons of Australia, who brought the mortality to amazingly low limits by persuading pediatricians and practitioners to refer cases of intussusception early. One has only to compare the durations of symptoms of series reported in the United States with those of Australia and England to realize what is yet to be attained in this

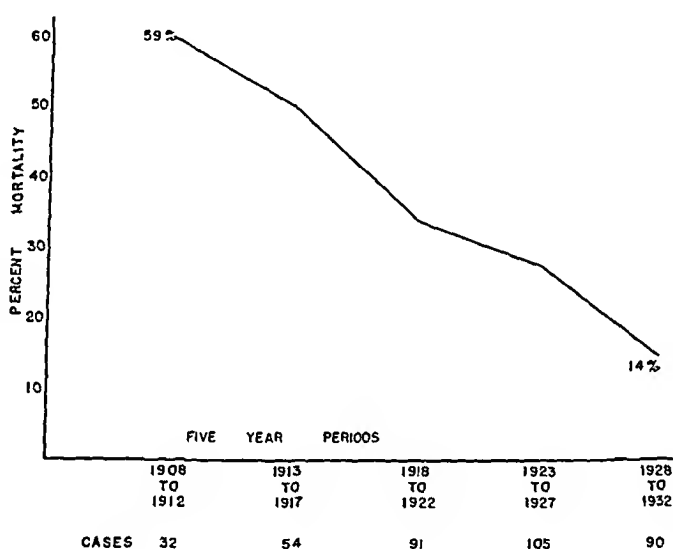


Fig. 6.—Mortality rates by five year periods, including all 372 cases.

country. Table 4 indicates the relation between the mortality in our series and the duration of symptoms, and figure 7 shows this relationship graphically.

Various authors have stated that if the children are seen within from twenty-four to forty-eight hours after the onset of symptoms the results are good. In our patients seen in the first thirty-six hours the mortality was 21 per cent for the first twenty-year period, whereas in the last five years we have had 60 such cases with no deaths.

Some of the reduction in mortality was unquestionably due to securing the cases earlier; formerly 52 per cent and recently 60 per cent were obtained in the first thirty-six hours. But improvement in the mortality rate has also been obtained by greater attention to postoperative care, for in table 4 it can be seen that in each of the time groupings (except one) there has been a reduction in the mortality in the second period as compared with the first.

Patients from private practice have always had a lower mortality than ward patients. In the first twenty year period there were 30 recoveries and 4 deaths, and in the last five years there were 10 recoveries and no deaths. In the private wing 80 per cent of the patients were seen within the first thirty-six hours—undoubtedly an important factor in decreasing the number of fatalities.

TABLE 4.—Duration of Symptoms and Corresponding Mortality Statistics

Duration of Symptoms	1908-1927			1928-1932		
	Living	Dead	Mortality, per Cent	Living	Dead	Mortality, per Cent
0 to 12 hours.....	55	4	7	25	0	0
12 to 24 hours.....	49	16	25	20	0	0
24 to 36 hours.....	12	11	49	5	0	0
36 to 48 hours.....	24	27	53	4	2	33
48 to 72 hours.....	15	15	53	3	2	40
72 to 96 hours.....	6	9	60	3	4	57
4 to 5 days.....	6	6	50	2	1	33
5 days and more.....	6	8	57	3	4	57
Time not stated.....	6	4	40	2	0	0
Totals.....	179	103	37	77	13	14

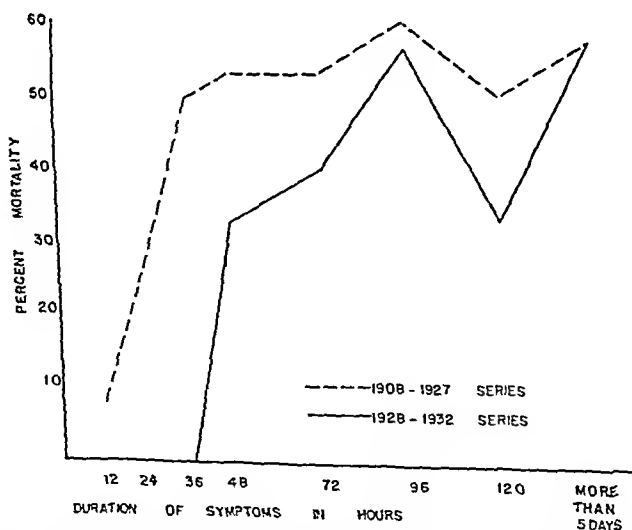


Fig. 7.—The relationship between the duration of symptoms and the corresponding mortality rates. The broken line represents the period from 1908 to 1927, and the solid line the period from 1928 to 1932.

In general, irrespective of the origin of the intussusception, the farther the mass progressed toward the anus, the higher was the related mortality (fig. 8). An exception to this rule has been those rare cases of colocolic type in which the mortality was somewhat lower owing to the fact that they gave early symptoms (rectal bleeding, etc.). This

increase in expectancy of death as the leading point approached the anus probably depended on increasing tension on the mesentery with resulting shock, vascular occlusions and greater difficulty in reduction.

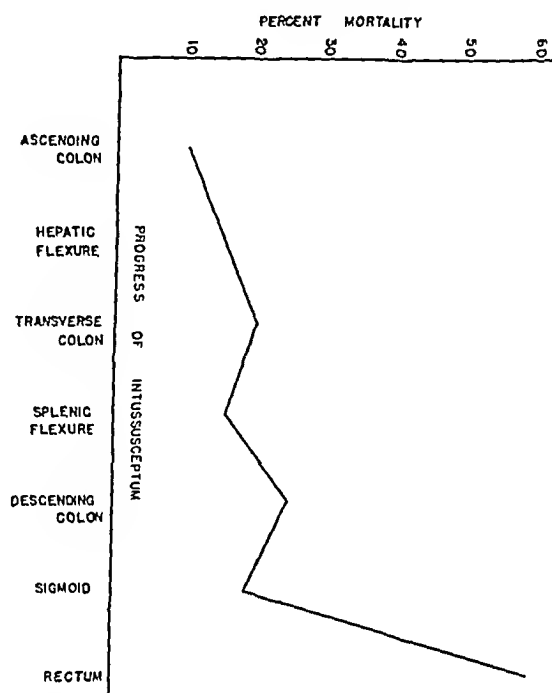


Fig. 8.—The relationship between the progress of the intussusceptum and the corresponding mortality rate, irrespective of the origin of the intussusception.

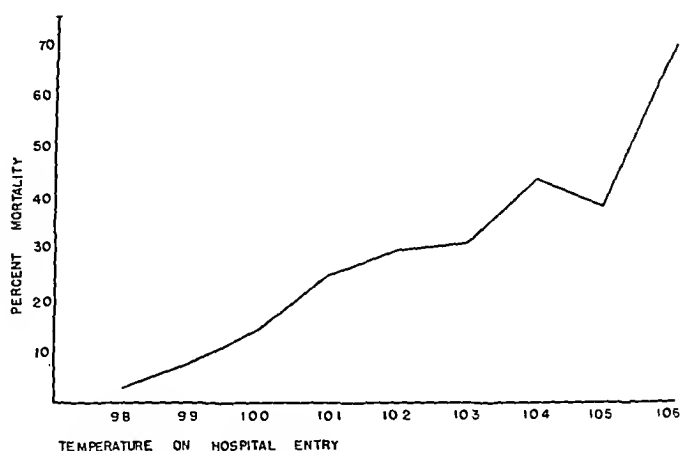


Fig. 9.—The relationship between the temperature on admission to the hospital and the corresponding expectancy of mortality.

The degrees of temperature had considerable prognostic value. Fever at the time of admission to the hospital was a bad sign, and with temperatures above 100 and 101 F. the expectancy of death rose rapidly. This is illustrated in figure 9. After operation practically all patients

had some fever for three or four days, which then subsided to normal temperature if there were no complications. A rise to 102 or 103 or even 104 F. was not unusual, but levels above 105 F. carried a grave and usually fatal prognosis.

#### PREOPERATIVE AND POSTOPERATIVE CARE

Everything possible was done to expedite operation. In the average cases no preoperative parenteral administration of fluid was practiced, but in the presence of marked dehydration dextrose was administered intravenously (10 cc. of 10 per cent solution of dextrose per pound of body weight) and saline solution subcutaneously (15 cc. of isotonic saline solution per pound of body weight). During operation a baby or young child was always wrapped with cotton batting to cover the arms, legs and chest completely. A hot water bottle was placed under the back to help prevent the loss of body heat. Atropine (without morphine) was given preoperatively, 1/1,000 grain (0.00006 Gm.) for patients under 1 year, 1/500 grain (0.00013 Gm.) for those between 1 and 2 years and correspondingly larger doses for older patients. Some English surgeons use heroic doses up to 1/150 grain (0.00043 Gm.) for infants, but we found no beneficial effect on the intestines from such doses, and hence employed the drug only for its action on the respiratory and salivary systems.

If no fluids had been administered before operation, they were immediately given as a routine when the child was returned to bed. The administration of fluids was repeated twice daily until dehydration was overcome and until adequate fluid was taken by mouth. Usually the parenteral administration of fluids was not repeated after the second postoperative day, but we have repeated it daily for from four to five days when indicated. By rectal tap 5 per cent dextrose was administered on return from the operating room and every four hours throughout the first postoperative day.

For the first postoperative day, or as long as there was vomiting, fluids without milk were offered every two or three hours. After vomiting had ceased, milk and whey were given, mixed in equal quantities, for an additional eighteen to twenty-four hours. Breast milk or a substitute was then given, but the full caloric or volume intake for the age and weight was not given until the fourth or fifth day. English surgeons offer the breast to suckling infants in from four to six hours after operation, but we do not like to give whole milk at such an early time, when there is danger of postanesthetic vomiting and aspiration.

*Postoperative Complications.*—Shock, dehydration and toxicity took the largest toll, and fully four fifths of those who died had these factors listed as the cause of death. Because such conditions caused most of

the fatalities, 85 per cent of the deaths occurred within forty-eight hours after entry into the hospital.

Peritonitis accounted for 6 deaths. This figure would probably have been higher had more autopsies been permitted. Bronchopneumonia was the cause of death in 5 patients, 2 of these having had advanced pneumonia at the time of entry into the hospital. Two patients had evisceration of the intestines when the wounds broke open on the tenth postoperative day. The wounds were resutured, but both patients succumbed one and two days later, respectively. Two other patients had poorly healing wounds, and because of impending evisceration the wounds were resutured successfully.

Not infrequently diarrhea developed during convalescence. This was probably due to secondary enteritis, and since the traumatized intestinal tract was more susceptible to infection, strict precautions had to be taken to guard against exposure to patients with dysentery. When such a complication developed, the oral intake was reduced, sedatives were given and fluids were administered parenterally.

#### SUBACUTE AND CHRONIC INTUSSUSCEPTION

Subacute intussusception has been defined as that in which the symptoms last for from five or six days to two weeks, and the chronic type as that in which the symptoms last for more than two weeks. In the first group there were 15 patients, 5 of whom lived and 10 of whom died. Only 1 had any demonstrable cause for the invagination (cecal polyp, recovery). In the chronic class 4 recovered and 1 died, and none had any demonstrable etiologic factor. In the two groups 3 patients were 3 years and 9 months, 6 years and 1 month and 9 years old, respectively, the remainder being 13 months old or younger. That these patients lived so long must have been due to the presence of incomplete intestinal obstruction and to the maintenance of the blood supply to the intussusceptum. Naturally, from only partial obstruction the symptoms were not so pronounced or so fulminating as those from acute intussusception, in which the bowel was usually completely occluded.

#### RECURRENT INTUSSUSCEPTION

In 1932 Thorndike reported 5 cases of recurrent intussusception from the Children's Hospital, Boston, and collected 75 more from the literature. He did not include the 9 cases of recurrent intussusception of Hipsley. Two other cases have been the subject of medical writings since then. With 2 additional cases which we have observed there have been at least 93 such cases.

In none of the 7 recurrent cases in our series was a mechanical cause found for the intussusception. No death has occurred in the recurrent cases. The time of recurrence varied from two months to three years after the initial attack. Six of the patients had one recurrence, and in each case only simple reduction was done. In one instance the appendix was also removed. The seventh patient had one recurrence for which reduction was performed, but following this there were three attacks suggestive of intussusception, in each of which there was apparently a spontaneous reduction. At exploration after the last attack no etiologic factor was found.

In the cases recorded in the literature the longest interval before recurrence was eight years and the shortest interval was thirty hours. The largest number of recurrences ever reported were in one of Hipsley's patients, who had six attacks after operative reduction.

Because of the relatively low incidence of recurrence, 1.8 per cent in our series, we believe that no time should be wasted at the primary operation in attempting procedures designed to prevent recurrence. A further reason for not undertaking any such operative procedure is the fact that a recurrence does not necessarily take place in the same location as the original intussusception. Thus, in Gray's case, with three attacks intussusception occurred in three different places. If there is any suspicion of an etiologic factor, such as a long mesentery, an abnormally mobile cecum, Meckel's diverticulum, a polyp, etc., it is better, if possible, to correct such abnormalities at a subsequent date when the patient is in better condition.

#### SUMMARY

Three hundred and seventy-two cases of intussusception are reported from the Children's Hospital, Boston.

Eighty-seven per cent of the patients were under 2 years of age, and 70 per cent were between the ages of 4 and 11 months. Sixty-one per cent were boys and 39 per cent were girls.

In only 5 per cent of the series were there demonstrable etiologic factors.

The important and most frequent symptoms were attacks of abdominal pain, pallor, sweating, vomiting and bloody stools occurring in a previously healthy child. The prominent physical findings were shock, dehydration, a palpable abdominal mass, blood from the rectum and possibly a mass palpable by rectal examination. Roentgen observations in the ileocolic variety were characteristic, but roentgen study was not necessary in the average case of acute intussusception.

The treatment was by operative reduction, and resection when reduction failed. Of 30 resections only 2 were successful. During the last five years, however, only 2 resections have been necessary in a series

of 90 cases. The mortality in all cases, in five year periods, has taken a continuous downward trend from 59 per cent in the 1908-1912 group to 14 per cent in the 1928-1932 group. In the last five years 60 cases were seen within thirty-six hours after the onset of symptoms and in all operation was performed without mortality.

It is believed that removal of a Meckel diverticulum or other cause of intussusception should be deferred if possible for a second operation.

Various factors and their relationship to the mortality are discussed. These include ranges of temperature, duration of symptoms, types of practice (private and charity) and location of the intussusception.

The preoperative and postoperative care are described.

Twenty cases of subacute and chronic intussusception are included, with a duration of symptoms varying from six days to eight weeks.

Seven cases of recurrent intussusception are included, an incidence of 1.8 per cent, without mortality.

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# INFLUENCE OF A LOCAL EXCESS OF CALCIUM AND PHOSPHORUS ON THE HEALING OF FRACTURES

AN EXPERIMENTAL STUDY

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As a result of recent advances in physiologic chemistry, many normal and pathologic processes are being considered from a chemical standpoint rather than anatomically or physiologically. Among these processes the formation of new bone in normal growth and in the repair of injury is receiving considerable attention. By certain writers, notably Leriche in France and Bancroft in this country, the process of ossification has been divorced from the influence of cells and is regarded as a purely chemical reaction which takes place extracellularly in the tissues around a fracture.

Accompanying this changing view is the tendency to explain non-union on the basis of a general deficiency of calcium and phosphorus in the blood or a local deficiency of these elements at the site of the fracture. Hence some workers have attempted to influence the rate of healing of the bone by changing the concentration of calcium and phosphorus in the serum either by an alteration in the diet or by the administration of parathyroid extract-Collip; others have injected various salts of calcium and phosphorus at the site of fracture in the hope of accelerating the rate of repair.

That the calcification of rachitic bone in vitro depends on the character of the serum used or on the calcium and phosphorus content of an aqueous solution was shown by Shipley, Kramer and Howland.<sup>1</sup> They found that normal serum favored calcification, while rachitic serum did not permit it, and that calcification in an aqueous solution occurred most abundantly when the reaction and the content of calcium and phosphorus were those of normal serum. Further experimental and clinical evidence as to the importance of the concentration of calcium and

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This investigation was supported by funds from the Christine Breon Fund, the University of California.

1. Shipley, P. G.; Kramer, B., and Howland, J.: Studies upon Calcification in Vitro, *Biochem. J.* 20:379, 1926.

phosphorus in the blood was provided by Peterson.<sup>2</sup> This author concluded from determinations of serum calcium and phosphorus in seventeen cases of nonunion and nine case of fracture which united normally that:

No healing of the fracture takes place when the inorganic constituents, calcium and phosphorus, are so reduced that the product of these elements is less than thirty; little healing takes place between thirty and thirty-five; active healing results with a product between thirty-five and forty.

He drew similar conclusions from a study of fractures in dogs receiving normal diets and diets low in calcium and phosphorus.

Further clinical and experimental evidence was submitted by Tisdall and Harris,<sup>3</sup> who determined the serum calcium and phosphorus in normal human beings of all ages, in patients during the period of union of fractures and in dogs with fractures. These writers observed, "It is evident that a high concentration of phosphorus in the blood serum accompanies the deposition of bone salts during the periods of normal growth of bone and of repair of fractures." They further concluded:

In the healing of fractures, two mechanisms are at work; one concerned with the maintaining of an adequate supply of bone salts in the blood, and the other with the taking up of these salts from the blood, and their precipitation in the tissue between the ends of the bone. Of these, the latter is apparently the more important process.

Other work has been reported which throws doubt on the significance of variations in the serum calcium and phosphorus in the healing of fractures. Henderson, Noble and Sandiford<sup>4</sup> determined the serum calcium and phosphorus in twenty clinical cases of ununited fracture which were compared with a series of cases in which there were no fractures. In both series the product of the values for serum calcium and serum phosphorus fell between 30 and 35. These authors stated: "It seems unlikely that bone formation is solely a question of physical chemistry. We are too imbued with the philosophy of Haldane to deny an important rôle to the bone forming cells themselves." An investigation of the effect of changes in the blood chemistry on the healing of experimental fractures in dogs was made by Ravdin and Morrison.<sup>5</sup> Normal dogs were compared with those in which the serum

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2. Peterson, H. A.: A Clinical Study of Ununited Fractures with Special Reference to the Inorganic Bone-Forming Elements in the Blood Serum, *J. Bone & Joint Surg.* **6**:885, 1924.

3. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, *J. A. M. A.* **79**:884 (Sept. 9) 1922.

4. Henderson, M. S.; Noble, T. P., and Sandiford, K.: Ununited Fractures with Special Reference to the Chemistry of the Blood, *J. Bone & Joint Surg.* **8**:607, 1926.

5. Ravdin, I. S., and Morrison, M. E.: Ossification After Fracture, *Arch. Surg.* **17**:813 (Nov.) 1928.

calcium was raised by the administration of parathyroid extract or lowered by parathyroidectomy. These workers concluded. "We have not been able to prognosticate the rate of ossification after fracture from the calcium and phosphorus product, from the ion product or from the negative logarithm of the ion product."

A later study by Speed<sup>6</sup> along similar lines led to almost identical conclusions. This writer produced alterations in the blood calcium and phosphorus by changes in the diet of dogs and by parathyroidectomy. By this operation a decided delay in the healing of fractures was produced, but the dogs in which the serum calcium was raised or lowered by special diets showed normal healing.

Dragstedt and Kearns<sup>7</sup> reported experiments in which the repair of defects in the femurs of dogs was observed under three conditions, namely: (1) in normal dogs, (2) in dogs on which thyroparathyroidectomy had been performed and (3) in dogs to which parathyroid extract-Collip was given. They concluded that thyroparathyroidectomy delays the healing of a defect in the bone, although healing goes on at a normal rate if calcium is administered following this procedure. The administration of parathyroid extract-Collip in moderate amounts has little effect on the rate of healing, while large doses cause a definite impairment of healing.

In a study by Stocker<sup>8</sup> of the metabolism of minerals in fractures the patients with normal union showed a hypercalcemia and a normal content of phosphorus in the serum. Similar results were obtained in the patients with delayed union, although the hypercalcemia persisted for a longer period in the latter.

In the hope of influencing the rate of healing, many workers have injected various salts of calcium and phosphorus at the site of experimental fractures. Albee and Morrison<sup>9</sup> injected a suspension of tricalcium phosphate in a gap produced in the radius of a rabbit. The other radius, with a similar defect, served as a control. The average length of time required for union of the fracture treated with calcium phosphate was thirty-one days, as compared with the controls, which required an average of forty-two days.

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6. Speed, K.: *Blood Serum Calcium in Relation to the Healing of Fractures*, J. Bone & Joint Surg. **13**:58, 1931.

7. Dragstedt, C. A., and Kearns, J. E., Jr.: *Experimental Study of Bone Repair: Effect of Thyro-Parathyroidectomy and of the Administration of Parathormone*, Arch. Surg. **24**:893 (June) 1932.

8. Stocker, H.: *The Metabolism of Minerals and Its Relation to Internal Secretion in Fractures*, Deutsche Ztschr. f. Chir. **231**:714, 1931.

9. Albee, F. H., and Morrison, H. F.: *Studies in Bone Growth: Triple Calcium Phosphate as a Stimulus to Osteogenesis*, Ann. Surg. **71**:32, 1920.

Eden<sup>10</sup> attempted to heal an operative gap in the radii of rabbits by filling the defect with calcium phosphate or carbonate, but this proved to be an unfavorable filling material, because it was too difficult to absorb. He obtained better results by filling the defect in the radius with a gelatin which contained calcium.

Cretin<sup>11</sup> found that the injection of the various mineral elements of bone between the ends of experimentally produced fractures resulted in a marked acceleration of the formation of callus and bone. Murray<sup>12</sup> carried out similar investigations in which he filled a gap of 2.5 cm. in a dog's radius with sterile powdered calcium carbonate and calcium phosphate, which was followed by solid bony union. The use of sterile powdered calcium hexose phosphate also proved successful, and union was even more rapid if fibrin from the dog's blood was placed in the gap before adding the calcium salt.

The experiments of Rollo<sup>13</sup> indicate that the injection of calcium glycerophosphate into the tissues around a fracture in rabbits serves to stimulate the formation of callus and bone. He found that this substance facilitated the closure of the gap in partial diaphyseal resection, while in controls the evolution of the callus was impeded by the interposed muscle.

A few surgeons have injected various salts of calcium and phosphorus into human beings in the hope of securing an acceleration of bone repair. Murray<sup>14</sup> used powdered calcium triple phosphate and calcium carbonate mixed with blood to fill the defect following saucerization of an infected compound fracture of the tibia. Cotton<sup>15</sup> injected salts of calcium and magnesium at the site of the fracture in a few clinical cases, but drew no conclusions from these trials. In addition to his previously described experimental work, Eden<sup>10</sup> injected secondary sodium phosphate at the site of the fracture in three instances of delayed healing in human beings. Consolidation resulted in all of the cases, two of which presented fractures of the femur and one a fracture of the tibia. The same author injected calcium glycerophosphate at the site of a bone graft of the femur with a good result.

In the injection of various substances at the site of fracture to stimulate ossification, the attempt has been made in most instances to

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10. Eden, R.: Untersuchungen über Vorgänge bei der Verknöcherung, *Klin. Wchnschr.* **2**:1798, 1923.

11. Cretin, A.: Etudes sur la calcification normale, *Gaz. d. hôp.* **97**:946, 1924.

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13. Rollo, S.: Injection of Calcium Salts into Tissues Adjacent to Fractures under Pathologic Conditions, *Ann. ital. di chir.* **10**:1059, 1931.

14. Murray, C. R.: Delayed and Non-Union in Fractures in the Adult, *Ann. Surg.* **93**:961, 1931.

15. Cotton, F. J.: Dislocations and Joint Fractures, ed. 2, Philadelphia, W. B. Saunders Company, 1924, p. 39.

supply the elements which make up bone in their natural proportions. Some dispute exists as to the state in which calcium and phosphorus occur in bone. The orthophosphate of calcium, tricalcium phosphate or  $\text{Ca}_3(\text{PO}_4)_2$  is given by most textbooks as the formula for bone (Roscoe and Schorlemmer<sup>16</sup>). According to Bogert and Hastings<sup>17</sup> the composition of bone can be represented by the formula  $\text{CaCO}_3 \cdot n \text{Ca}_3(\text{PO}_4)_2$  in which  $n$  is approximately 2 in untreated bone. Quantitative determinations of calcium and phosphorus in powdered bone (Shear and Kramer<sup>18</sup>) indicate that the probable formula for bone salts is  $\text{CaHPO}_4$ , the dicalcium phosphate. As has been noted previously, the salts injected at the site of fractures include tricalcium phosphate, calcium glycerophosphate, calcium hexose phosphate, calcium carbonate, calcium in gelatin and secondary sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ). In the present study use has been made of the three calcium phosphates (tricalcium, dicalcium and monocalcium) and of calcium glycerophosphate.

#### METHODS

An operative defect, between 0.5 and 1 cm. in length, was made in the radii of seventeen rabbits. One side served as a control, while the defect in the opposite radius was filled with a dry, powdered salt of calcium and phosphorus. In a few cases, a suspension of the salt was injected at the site of the fracture a few days after the segment of radius was excised. The rate and extent of the callus formation were observed in roentgenograms taken at weekly intervals following the operations. The animals were killed from three to ten weeks after operation, and a microscopic examination of each radius was made.

The following salts of calcium and phosphorus were used:

Monocalcium phosphate	$\text{Ca}(\text{H}_2\text{PO}_4)_2$	4 experiments (17, 18, 20, 22)
Tricalcium phosphate	$\text{Ca}_3(\text{PO}_4)_2$	6 experiments (71, 72, 73, 74, 75, 76)
Dicalcium phosphate	$\text{CaHPO}_4$	2 experiments (77, 78)
Calcium glycerophosphate		5 experiments (81, 82, 83, 84, 85)

#### RESULTS

The results obtained from these experiments are best considered under four headings, depending on the salt which was used.

*Monocalcium Phosphate.*—In rabbit 17 both defects became filled with new bone, although union was somewhat delayed on the side in which the defect was filled with monocalcium phosphate. In experiment 20 the defect in the left radius was filled with the salt at the time of operation, while the defect in the right radius served as a control.

16. Roscoe, H. E., and Schorlemmer, C.: *Treatise on Chemistry*, New York, The Macmillan Company, 1913, vol. 2, p. 557.

17. Bogert, L. J., and Hastings, A. B.: *Calcium Salts of Bone*, J. Biol. Chem. 94:473 (Dec.) 1931.

18. Shear, M. J., and Kramer, B.: *Composition of Bone*, J. Biol. Chem. 79:105, 1928.

The animal died twenty-three days later, at which time there was an extensive abscess in the left foreleg, and the muscles appeared necrotic. Roentgenograms (fig. 1) showed that the gap in the right radius was partially filled with callus, while no closure of the defect was seen in the left radius. Microscopic sections through the two defects (fig. 2) revealed an abscess at the site of the defect in the left radius, while the gap in the opposite radius was filled with cartilage and early callus. In experiment 18 the defects were filled with bone chips on the right side and with monocalcium phosphate on the left. Union occurred in the former after twenty-one days and on the side containing the salt only after forty-two days. In the other case in which the salt was used, the rabbit (22) died on the third day with no evidence of healing in either radius.

*Tricalcium Phosphate.*—The results in the six experiments in which tricalcium phosphate was placed in the defect of one radius fall into two equal groups: In the first, which consisted of experiments 71, 72 and 73, both radii healed in approximately the same length of time. The second group, which consisted of experiments 74, 75 and 76, showed complete although delayed healing of the defect in the radius in which tricalcium phosphate had been placed, while the other defect, containing no salt, failed to close. There was no variation in the methods employed in these six experiments to account for the difference in results. As an example of the first group, experiment 72 showed an equal rate of callus formation on the two sides, as revealed by roentgenograms (fig. 3), and in microscopic sections (fig. 4) both radii presented the same appearance. In the second group, roentgenograms (fig. 5) in experiment 76 showed a complete closure of the defect containing tricalcium phosphate, while typical nonunion occurred in the opposite radius. Microscopic sections (fig. 6) substantiated the conclusions drawn from the roentgenograms.

*Dicalcium Phosphate.*—The dicalcium phosphate was employed in two instances, in both of which union occurred in both radii at approximately the same time. In one of these experiments (78), roentgenograms (fig. 7) showed that the defect in each radius was fairly well filled after three weeks and firmly united after six weeks. In microscopic pictures (fig. 8) the same appearance of complete restoration of the cortex was seen in both radii.

*Calcium Glycerophosphate.*—This salt was used in five rabbits, two of which died in less than one week. In the three rabbits which lived until union occurred, the slight difference in the rate of healing favored the side in which no salt was placed. Figure 9 shows the rate of healing as indicated roentgenologically, and figure 10 presents an almost identical appearance of the two radii eight weeks after operation (experiment 82).

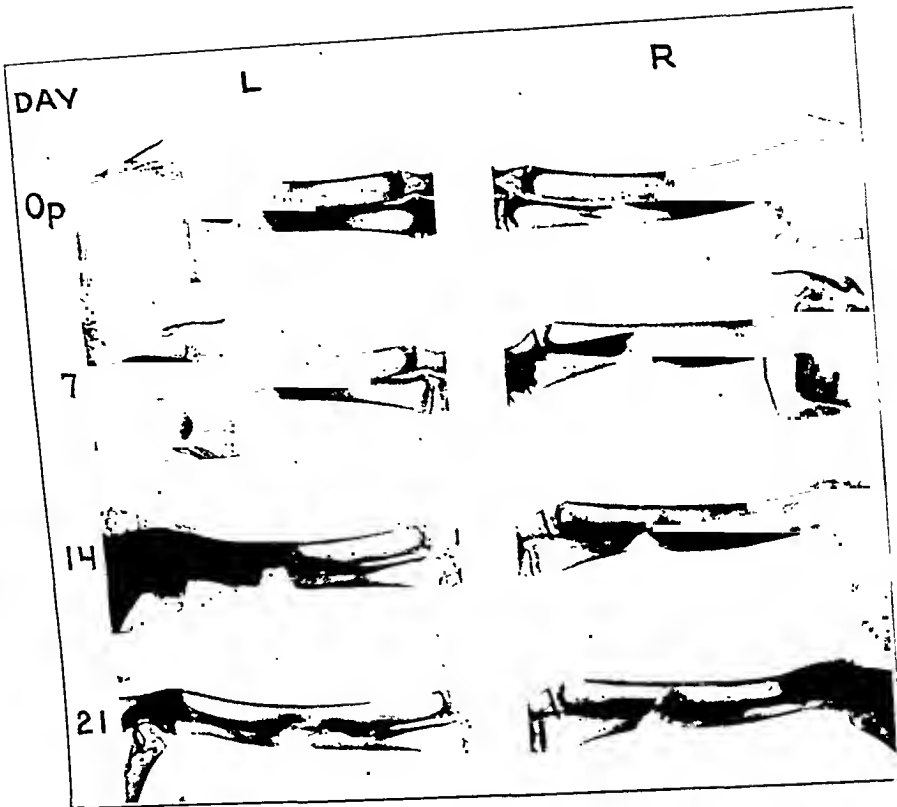


Fig. 1.—Roentgenograms in experiment 20.

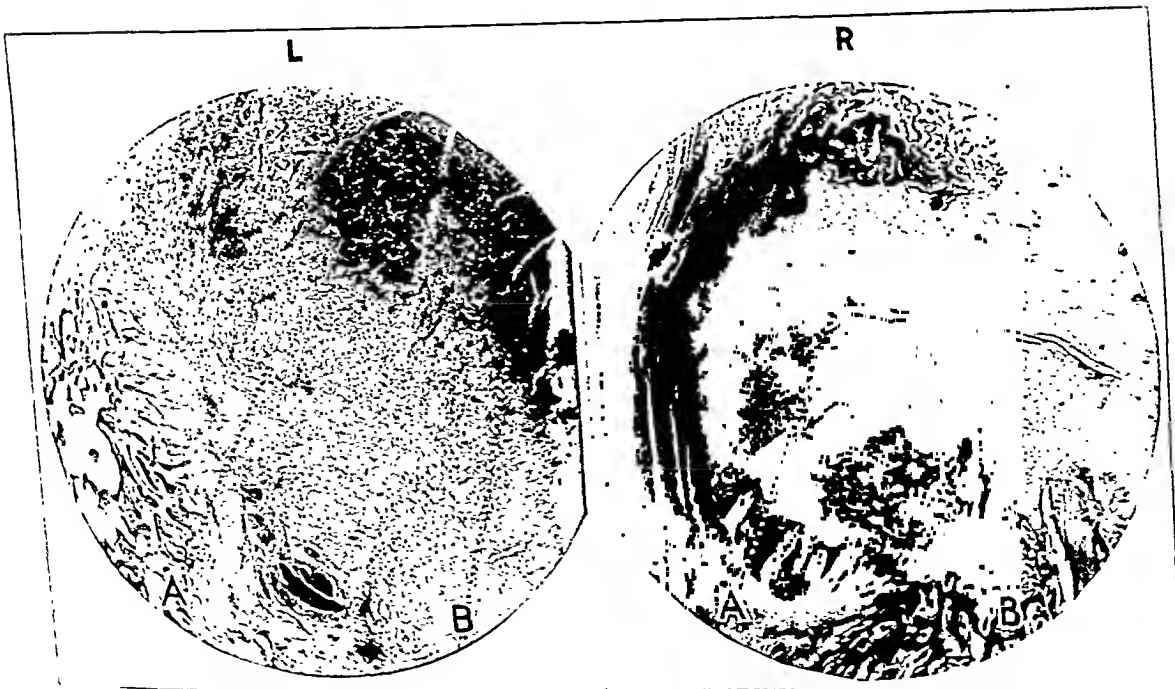


Fig. 2.—Photomicrographs of fracture site in experiment 20. In the section of the left radius (*L*), *A* indicates necrotic muscle and *B* an abscess; in the section of the right radius (*R*), *A* indicates cartilage and *B* old cortex.



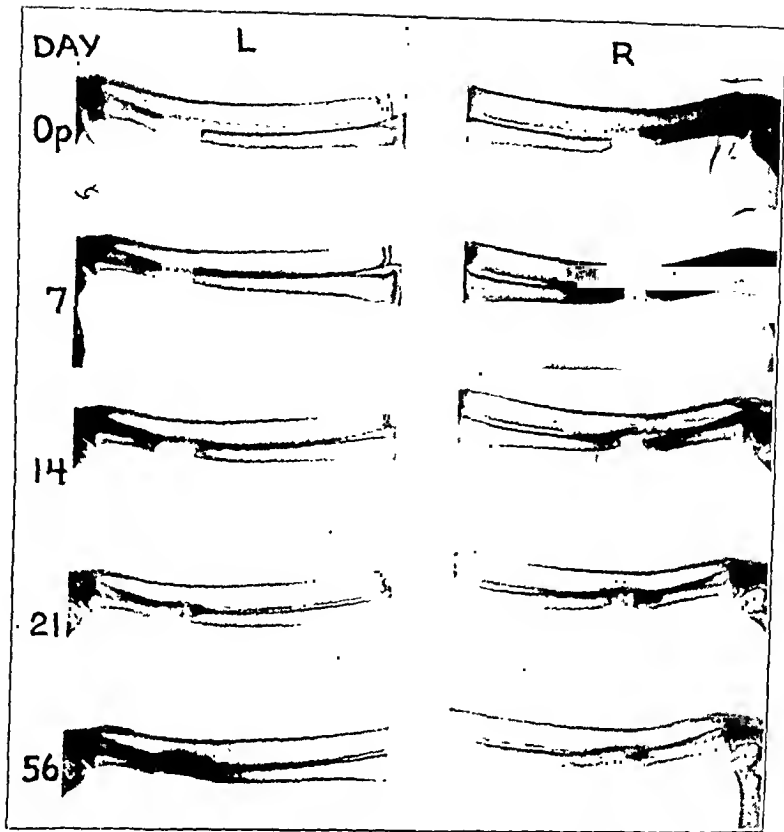


Fig. 3.—Roentgenograms in experiment 72.

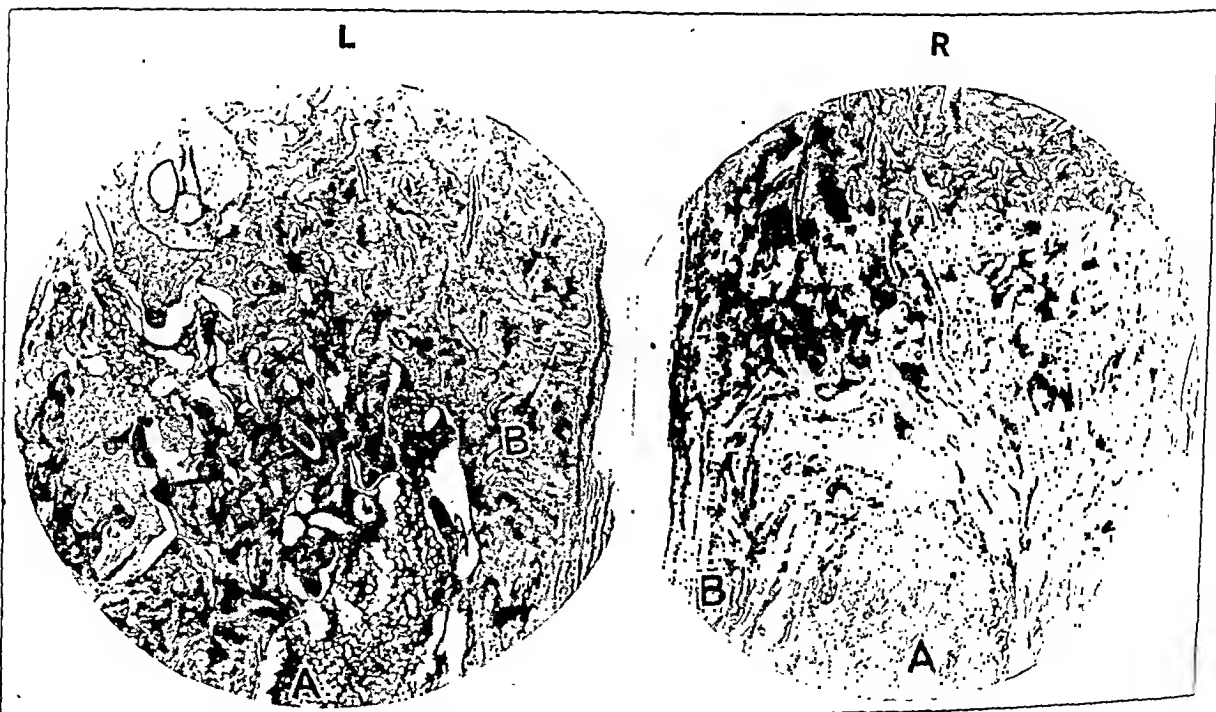


Fig. 4.—Photomicrographs of the site of fracture in experiment 72. *A* indicates marrow and *B* new cortex.

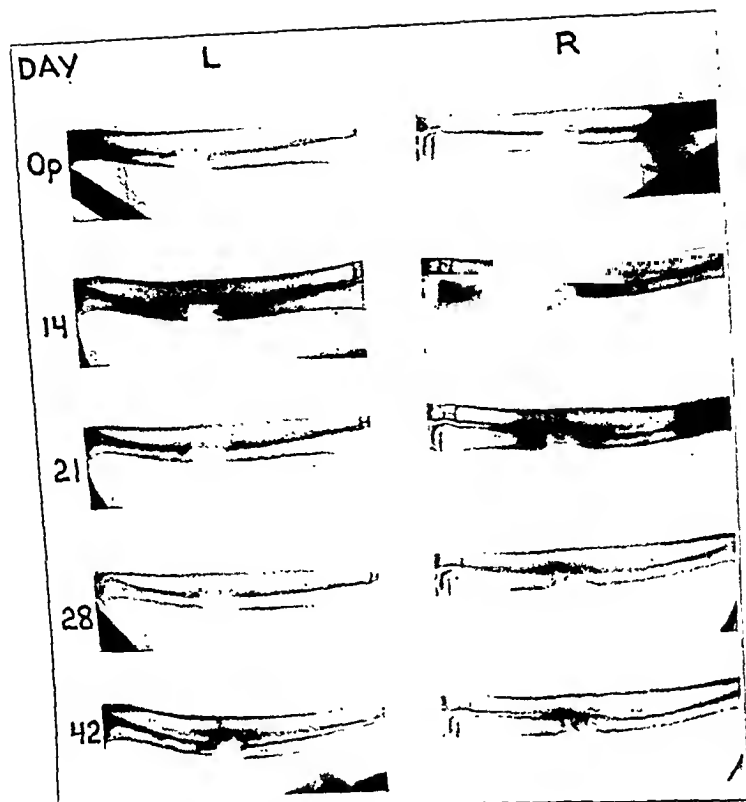


Fig. 5.—Roentgenograms in experiment 76.

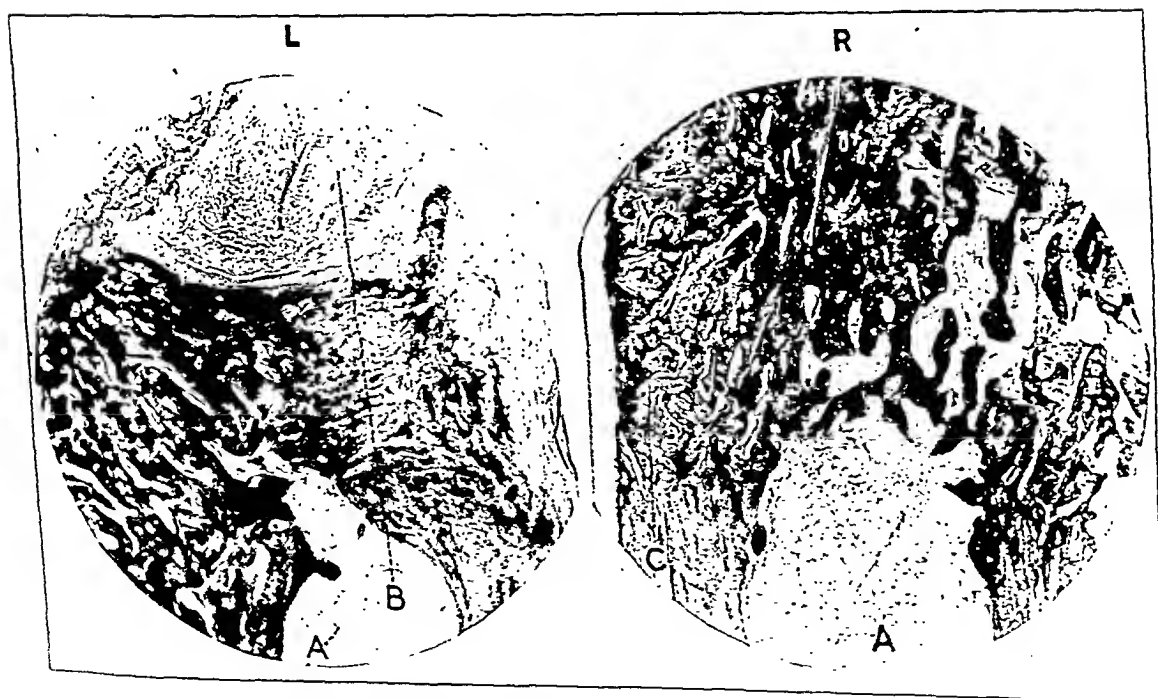


Fig. 6.—Photomicrographs of the site of fracture in experiment 76. *A* indicates marrow; *B*, the defect; *C*, cortex.

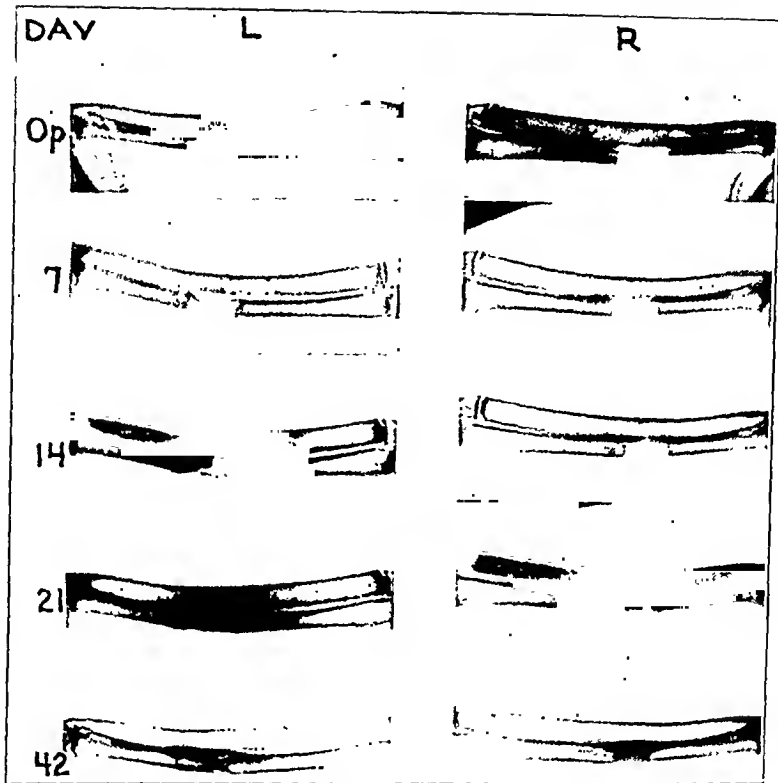


Fig. 7.—Roentgenograms in experiment 78.

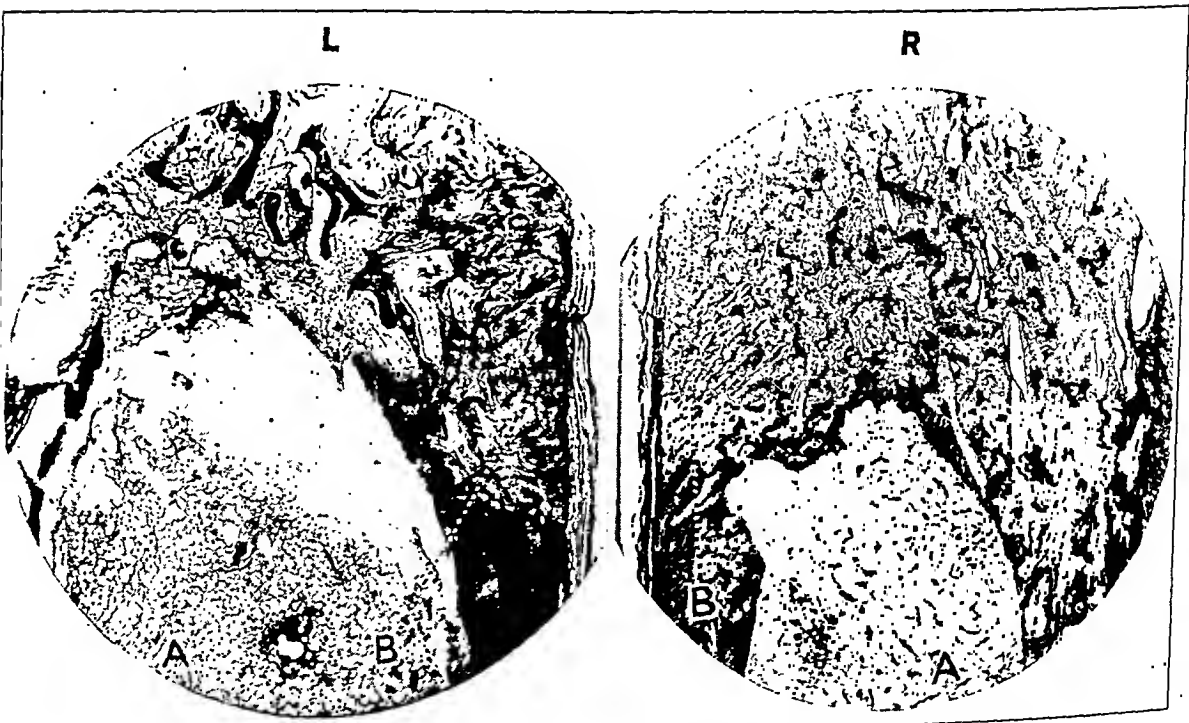


Fig. 8.—Photomicrographs of the site of fracture in experiment 78. *A* indicates marrow and *B* new cortex.

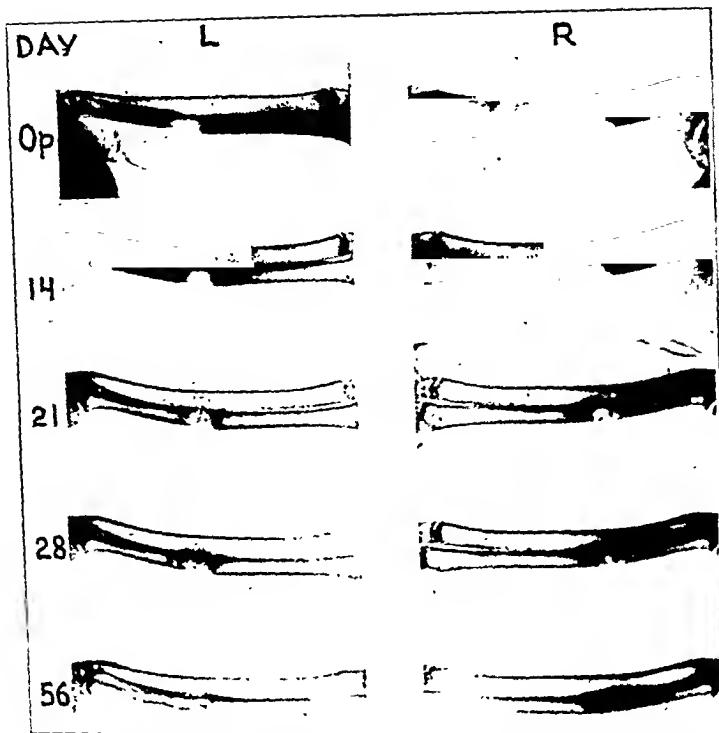


Fig. 9.—Roentgenograms in experiment 82.

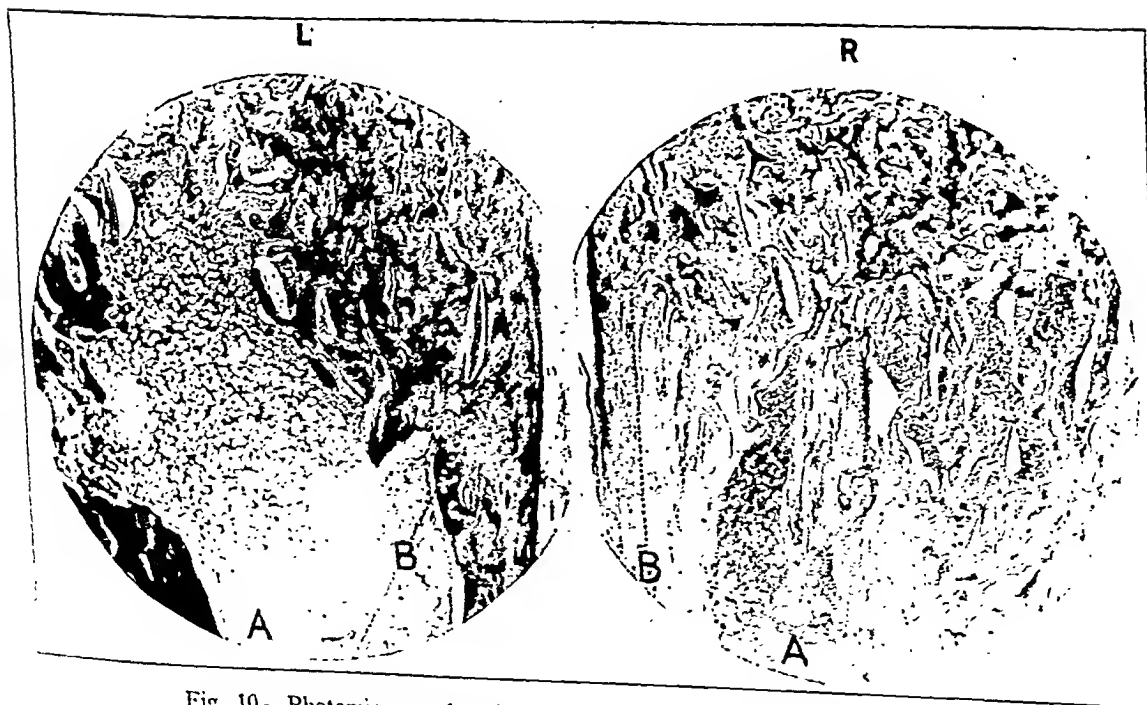


Fig. 10.—Photomicrographs of the site of fracture in experiment 82. *A* indicates marrow and *B* new cortex.

## SUMMARY

The rôle of calcium and phosphorus metabolism in the healing of fractures has long been a subject for discussion and investigation. Certain workers have emphasized the importance of calcium and phosphorus as found in the blood serum, while others have turned their attention more to the local concentration of these minerals at the site of the fracture. Concerning the influence of increased serum values, opinion and evidence seem about equally divided. On the other hand, an excess of the local supply of these salts is reported almost unanimously as accelerating the rate of union. The present work has been limited to the influence of the latter when present throughout the period of healing of a defect in the radii of apparently normal rabbits.

After the use of three forms of inorganic calcium and phosphorus and one organic compound, healing was delayed in five rabbits and uninfluenced in seven; two rabbits died in the first week after operation, and in three of the rabbits in which tricalcium phosphate was added, the healing was delayed on both sides, although complete union eventually resulted on the treated side, while the control defects went on to typical nonunion. The reason for this delay is not apparent. However, the conclusion seems justified that in certain cases of delayed union tricalcium phosphate is an aid to union.

None of the calcium and phosphorus compounds used in excess seemed capable of accelerating the normal rate of healing. In this respect the results fail to follow the well recognized chemical law that increasing the concentration of the reacting substances speeds up the reaction. Because of this fact, it is probable that the process of ossification is more than the purely chemical equation which certain writers describe.

## CONCLUSIONS

1. In normal healing under favorable conditions the continued presence of an excess of calcium and phosphorus at the site of fracture either did not influence the rate of union or retarded it.

2. In delayed healing resulting from unknown causes the presence of tricalcium phosphate at the site of the fracture appeared to favor the union.

3. In no case did the presence of monocalcium phosphate, dicalcium phosphate or calcium glycerophosphate have a favorable influence.

# COMPARATIVE VALUE OF INTRAVENOUS SCLEROSING SUBSTANCES

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AND

HOWARD MAHORNER, M.D.

NEW ORLEANS

In a previous communication, Garside and one of us (A. O.)<sup>1</sup> reported the results of studies on the effect of the intravenous injection of certain sclerosing solutions. The present paper is in reality a report of the continuation of that work, comprising a similar study of nine additional solutions. The twenty solutions in the first study and the nine in the present study include practically all the important drugs advocated for use in the treatment of varicose veins by injection and in addition certain new drugs that have not been used before for this purpose, either experimentally or clinically. Comparison of the results shows the relative value of the solutions in their potency as thrombosing agents producing changes in the walls of the veins.

The solutions used in this investigation were 10 and 5 per cent solutions of sodium morrhuate (our own); 5, 3 and 2 per cent solutions of sodium gynocardate; 5, 3 and 2 per cent solutions of sodium hydnocarpate, and a 5 per cent solution of sodium morrhuate (Searle). Our own sodium morrhuate was prepared in the chemical laboratory of the department of surgery. The solutions of sodium gynocardate, sodium hydnocarpate and our own sodium morrhuate were dissolved in physiologic solution of sodium chloride. Searle's sodium morrhuate is prepared in benzyl alcohol.

Sodium morrhuate is obtained from cod liver oil, whereas sodium gynocardate is prepared from chaulmoogra oil, and sodium hydnocarpate from an oil closely resembling chaulmoogra oil, obtained from the seed of a tropical tree, *Hydnocarpus wightiana*.<sup>2</sup>

## METHOD

The method of study was that used by Garside and one of us (A. O.).<sup>1</sup> Dogs were selected as the test animals. Veins in each of the four legs were used.

From the Department of Surgery, Tulane University School of Medicine.

1. Ochsner, Alton, and Garside, Earl: *The Intravenous Injection of Sclerosing Substances*, *Ann. Surg.* 96:691, 1932.

2. Sodium gynocardate and sodium hydnocarpate were used because of a suggestion made by Sir Leonard Rogers (*Intravenous Sclerosing Injections*, *Brit. M. J.* 2:120, 1930).

In the hindlegs, four injections were made into the long saphenous veins. The levels of injection were: (1) at the dorsum of the foot, (2) at the ankle, (3) at the middle third of the leg and (4) at the level of the knee. In the forelegs injections were made into the antebrachial cephalic veins<sup>3</sup> (1) at the level of the paw, (2) at the level of the wrist, (3) at the middle third of the foreleg and (4) at the level of the elbow joint. Thus, in each dog there were sixteen injections, four in each leg, but only one drug was used in any one leg, though it was injected at four different levels. Generally a different solution was used for each leg. After the injection was completed, a ring was marked around the area of injection with a moistened silver nitrate stick. This method of marking was satisfactory, and it enabled us subsequently to remove with accuracy the vein into which injection was made at the level of the injection.

Each drug was injected sixteen times, so for each drug sixteen portions of vein were subsequently removed, representing different periods of time elapsed after the injection of the drug. The time intervals at which portions were removed after the injection of each solution were: one-half hour, one, three, six, twelve, twenty-four and forty-eight hours; three, four, six, ten, fourteen and twenty-one days, and four, six and eight weeks.

In removing the vein sections the area encircled by the silver nitrate mark was infiltrated subcutaneously with procaine hydrochloride. A longitudinal incision about 2 cm. in length was made over the course of the vein, the vein was identified, and the surrounding tissues, including the nerve, were carefully dissected free from it, caution being taken not to dislodge a thrombus from the lumen of the vein. The vein was clamped at each end of a segment (proximal end first) about 1 cm. in length, and the intervening segment was removed. The vein was then ligated proximal and distal to the clamps, and the wound was closed with silk. In removing the sections, the more distal one was always removed first and then in succession the more proximal segments. It was presumed that removal of the segments at different times would not dispose to thrombosis by interfering with the return of blood, even if we must admit the slight possibility that removal of some *vis a tergo* might result in propagation of a thrombus to the next higher level. The belief that thrombosis at the next higher level did not occur because of this was supported by the fact that invariably the longer "intervals" sections showed lower percentages of thromboses than did the earlier sections; and one would have expected the opposite, had the theoretical reason been an actual fact. Moreover, the findings in veins showing changes were quite constant for the different periods. We believe that we can explain this lower percentage of thrombosis after the longer periods by reasons other than inaccuracies.

The veins were prepared for microscopic study by cutting cross-sections and staining them with hematoxylin and eosin and Mallory's connective tissue stain, and in some instances with Verhoeff's elastic tissue stain.

In studying the sections microscopically, the results were recorded in four grades representing different degrees of change: from 0 to 25 per cent, grade I; from 25 to 50 per cent, grade II; from 50 to 75 per cent, grade III, and from

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3. Ellenberger, W., and Baum, H.: *Anatomie des Hundes*, Berlin, Paul Parey, 1891.

75 to 100 per cent, grade IV. The observations were divided in the following manner:

1. The lumen
  - (a) Thrombosis
2. The intima
  - (a) Endothelial destruction
  - (b) Exposure of nuclei
  - (c) Vacuolation of cells
  - (d) Pyknosis
3. The internal elastic lamina (whether it was intact or had been completely or partially destroyed)
4. The media
  - (a) Edema
  - (b) Leukocytic infiltration
  - (c) Hemorrhage
  - (d) Connective tissue proliferation
  - (e) Presence of new blood vessels
  - (f) Hyaline degeneration and coagulation necrosis of the muscle
  - (g) Atrophy of the muscle
5. The adventitia
  - (a) Edema
  - (b) Hemorrhage
  - (c) Presence of new blood vessels
  - (d) Leukocytic infiltration
  - (e) Hyperemia
  - (f) Connective tissue proliferation

The grades I to IV of the thrombus indicate whether the thrombus completely occluded the lumen (grade IV), as it generally did if it was present, or whether it only partially occluded the lumen. Moreover, the grade of organization was studied in each thrombus. When the organization was just beginning, it was graded I. When the connective tissue cells had advanced halfway to the center of the clot, organization was graded II. When the connective tissue cells had advanced to the center but recanalization did not seem to be complete, it was graded III, and when fibrosis and recanalization seemed to be complete, it was graded IV.

Endothelial destruction was graded on the percentage of the endothelial cells that had completely disappeared. The two most important criteria as to the sclerosing value of the various substances were the presence of a thrombus and the destruction of endothelial cells.

The grading of the other changes is in each instance an individual evaluation of the percentage of the change occurring. Such a method is not strictly mathematically accurate and has an associated percentage of error. However, as one of us (A. O.) had also studied the slides in a previous analogous study<sup>1</sup> of twenty sclerosing substances, the results in the two investigations are comparable, and it is possible to indicate the most effective of the twenty-nine solutions.

#### CHANGES IN THE INTIMA

Some sclerosing substances injure the cell by dehydration, e.g., hypertonic salt and sugar solutions; others, by direct chemical injury.



We have observed these changes in fixed subcutaneous tissue in another study of the action of sclerosing substances on tissues and will report the results in a subsequent paper. When the intimal cells are sufficiently injured, they become detached and are carried away by the blood stream. It is destruction of the intima which results in the precipitation of a thrombus. Sclerosing substances do not hasten the coagulation time of the blood. We have proved this with adequate control in vitro by the addition of 0.5 cc. of quinine and urea hydrochloride to 1 cc. of freshly drawn blood. The coagulation time was not reduced, but slightly lengthened. The same result was obtained with Searle's sodium morrhuate.

*Pyknosis.*—One of the earliest appearances that may give evidence of a retrogressive change in the cell is a more densely staining nucleus. Slight grades of such a change are difficult to distinguish from the normal appearance of the cell, and it is probable that fixing and staining may produce some of the changes which appear to be pyknosis, karyolysis or karyorrhexis. In some instances we observed pyknosis in a vessel which otherwise appeared to be normal and in sections removed at long intervals after the injection of sclerosing substances. Such a change would throw some doubt on the value of a darkly stained small nucleus as a sign of injury by the sclerosing solution. It possibly indicates that the changes we record as pyknosis occurred after the vessel had been removed from the animal. Sometimes the higher percentages of pyknosis occurred in the series of veins into which drugs were injected which caused the lowest percentage of endothelial destruction and thrombosis. Sodium hydncarpate, 2 per cent, showed 44 per cent pyknosis and 12.5 per cent thrombosis, whereas 5 per cent sodium gynocardate showed an average of 25 per cent pyknosis with 50 per cent thrombosis. This is explained by the fact that when thrombosis occurs the intima is partially or completely absent, and thus in the averaging of results instead of there being sixteen veins to show pyknosis there are in reality fewer.

*Vacuolation.*—This change (fig. 1) appears to be an intracellular edema and was irregular and inconstant. It was present in some sections of veins which had been treated with practically every one of the nine solutions under consideration. Its significance, like pyknosis, is difficult to interpret, and comparison of the average vacuolation occurring from the different agents leaves no clue as to the meaning. It is not necessarily an early change, as with our own sodium morrhuate solution vacuolation did not occur in the sections removed one-half hour or six hours after injection (sections removed one and three hours after injection showed marked endothelial destruction), but it did occur in the sections removed forty-eight hours, three days and fourteen days after

injection, being absent in all others. Such irregularities in the occurrence of vacuolation may be found in the results of almost any of the sclerosing agents.

*Exposure of Nuclei.*—By this change we mean that the cytoplasm on the free side of the endothelial cells lining the lumen of a vessel had been apparently completely destroyed or in some way removed so that

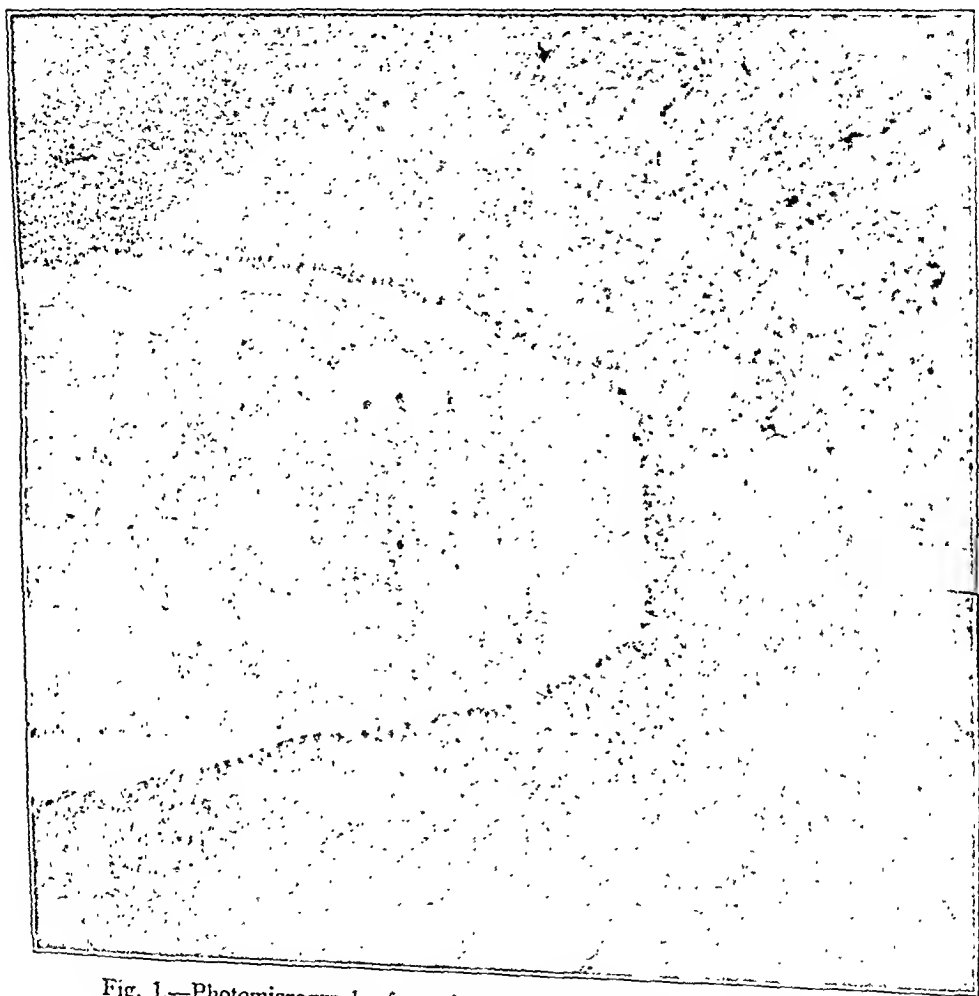


Fig. 1.—Photomicrograph of a vein showing vacuolation of cells of the intima forty-eight hours after the injection of 2 per cent sodium gynocardate.

the nucleus seemed to lie immediately under the cell membrane. Such a change was inversely proportional to the incidence of complete destruction of the endothelium. It was observed in some sections even when there were no other changes throughout the section, and it is not regarded as a reliable sign of injury resulting from the sclerosing substances.

*Thrombosis and Endothelial Destruction.*—Thrombosis did not occur in any instance in which there was no destruction of the endothelium.

Liberation of thrombokinase seems essential for precipitation of the thrombus. A graphic representation of the degree and incidence of thrombosis is shown in figure 2. A thrombus was present in 71 per cent of the sections of veins into which Searle's sodium morrhuate was injected, and endothelial destruction was present in the same percentage. Some endothelial destruction was present in 75 per cent of the sections of veins treated with 5 per cent sodium gynocardate, but thrombosis was present in only 50 per cent. However, endothelial destruction was graded IV in only 25 per cent of the sections treated with 5 per cent sodium gynocardate, whereas it was graded IV in 71 per cent of the sections treated with Searle's sodium morrhuate (figs. 2 and 3). Thus,

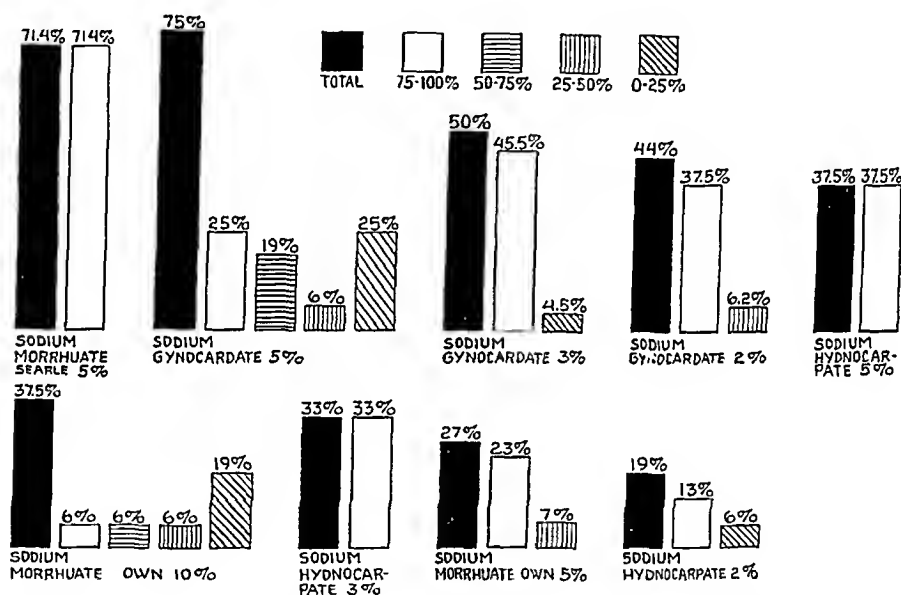


Fig. 2.—Graphic representation of the incidence and degree of endothelial destruction after intravenous injection of nine different sclerosing solutions. Four grades of destruction are indicated. Black represents the total destruction for each substance.

it would appear that experimentally Searle's sodium morrhuate is more effective than 5 per cent sodium gynocardate in producing destruction of the endothelium and thrombosis when injected into a vein. In their effectiveness in production of thrombosis the nine drugs used by us may be arranged as in figure 2. The effectiveness of the various solutions in producing thrombosis is as follows: Searle's sodium morrhuate, 71.4 per cent thrombosis; 5 per cent sodium gynocardate, 50 per cent; 3 per cent sodium gynocardate, 50 per cent; 2 per cent sodium gynocardate, 44 per cent; 5 per cent hydno carpate, 37.5 per cent; 5 per cent sodium morrhuate (our own), 33 per cent; 3 per cent sodium hydno carpate, 33 per cent; 10 per cent (our own), sodium morrhuate, 19 per cent; 2 per cent sodium hydno carpate, 12.5 per cent (fig. 4). The discrep-

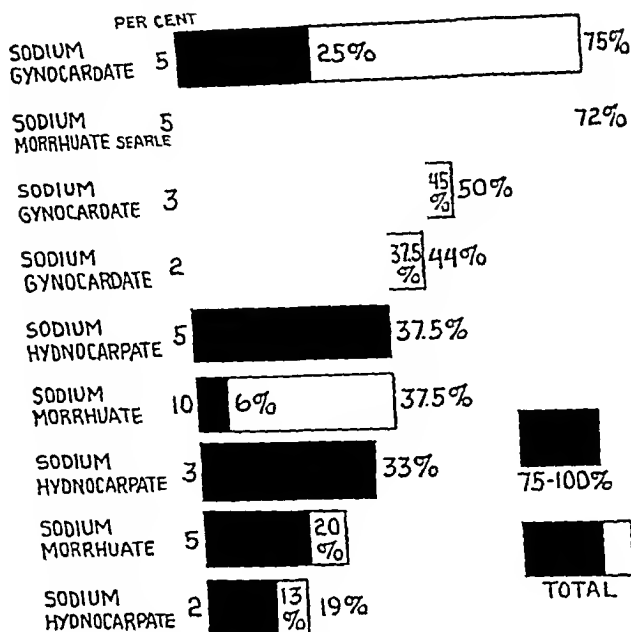


Fig. 3.—Graphic representation of comparative endothelial destruction produced by intravenous injection of sclerosing solutions. Black represents grade IV destruction of endothelium; the whole block, the total incidence of destruction of any grade whatsoever.

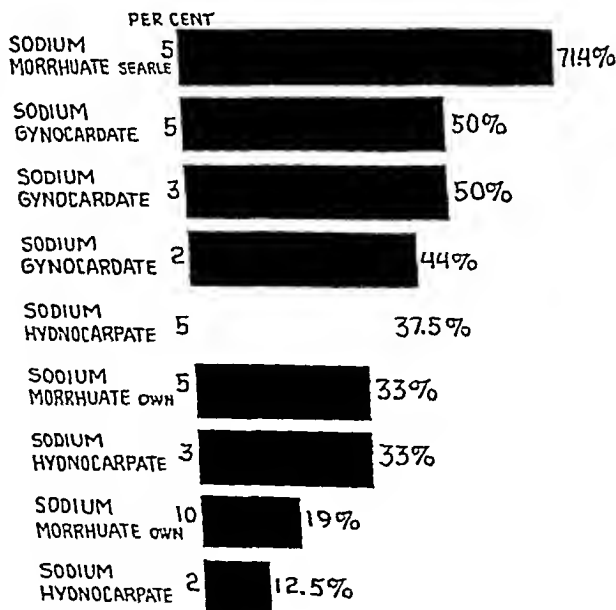


Fig. 4.—Graphic representation of relative thrombus-producing effectiveness of nine different sclerosing solutions.

ancy between the results obtained with our own 5 per cent sodium morrhuate (33 per cent thrombosis) and with Searle's 5 per cent sodium morrhuate may be due to the fact that in preparing our product we dissolved the sodium morrhuate in physiologic solution of sodium chloride, whereas Searle's sodium morrhuate is prepared with benzyl alcohol. It is possible that the benzyl alcohol enhances the sclerosing property of the sodium morrhuate. This is being investigated further.

When the three most effective thrombus-producing drugs in the study of Garside and one of us (A. O.)<sup>1</sup> are compared with those in the present series, three solutions in the latter series, Searle's sodium

PER CENT		
SODIUM MORRHUATE SEARLE	5	71.4%
SODIUM GYNOCARDATE	5	50%
SODIUM GYNOCARDATE	3	50%
SODIUM SALICYLATE *	40	47%
SODIUM GYNOCARDATE	2	44%
MERCURIC CHLORIDE *	1	41%
SODIUM HYDNOCARPATE	5	37%
QUININE & UREA HYDROCHLORIDE *	13	28%

Fig. 5.—Graphic representation of thrombus-producing effectiveness of eight intravenous sclerosing solutions selected from nine solutions studied by us and twenty studied by Garside and one of us (A. O.). Three solutions from the latter study are marked X.

morrhuate and 5 and 3 per cent sodium gynocardate, were more potent in producing thrombus than the most effective solution (sodium salicylate, 40 per cent) in the former series (fig. 5). Quinine and urea hydrochloride was only ninth in thrombus-producing effectiveness in the entire series.

We are somewhat at a loss to explain the fact that in practically all instances we found more thrombosis in the eight sections representing early periods after injection, i. e., from one-half hour to three days, than in the eight sections representing longer periods, i. e., from four days

to eight weeks. When the periods are thus separated into two groups, the following percentages were found for our four most effective drugs:

	Thrombosis in Sections	
	1st period	2d period
Searle's sodium morrhuate, 5 per cent.....	50	21.5
Sodium gynocardate, 5 per cent.....	31	19.0
Sodium gynocardate, 3 per cent.....	25	25.0
Sodium gynocardate, 2 per cent.....	25	19.0

This discrepancy is hard to explain. It is possible that in the process of repair a clot might not go on to complete fibrosis and organization, but that blood circulating apparently through an old clot, as has been described by one of us (H. M.),<sup>4</sup> might gradually remove the thrombus. Such a process does not seem probable in our present knowledge of thrombosis, but there are appearances in clots that are highly suggestive that this does occur.

*Organization.*—Organization of a thrombus in a vessel occurs according to a definite process which has been adequately described by numerous pathologists. In this study organization begins shortly after the thrombus is precipitated. Very definite evidence of the ingress of fibroblasts into the periphery of a thrombus is present after forty-eight hours (fig. 6). On the other hand, there was no evidence of organization in one section removed six days after injection. In this vein propagation of a thrombus probably occurred, and the section was cut across the last precipitated area. Organization with recanalization seems to be complete by the tenth to the fourteenth day (figs. 7 and 8).

#### DESTRUCTION OF THE INTERNAL ELASTIC LAMINA

Definite evidence of destruction of the internal elastic lamina was observed in some of the sections. In some instances it was simply raised out of position and projected into the lumen. In other instances it was fragmented; in still other sections it was completely absent (fig. 9). The normal elastic lamina was always intact when the endothelium had not been destroyed. Whenever there had been destruction of the lamina there was a clot in the lumen. However, the reverse was not true, viz., that destruction of the internal elastic lamina was always present when a clot was found. Searle's sodium morrhuate produced some injury to the lamina in the highest percentage of instances (35.6 per cent). Both 3 per cent sodium gynocardate and 5 per cent sodium hydncarpate pro-

4. Brown, G.; Allen, E. V., and Mahorner, H. R.: *Thrombo-Angiitis Obliterans*, Philadelphia, W. B. Saunders Company, 1928.

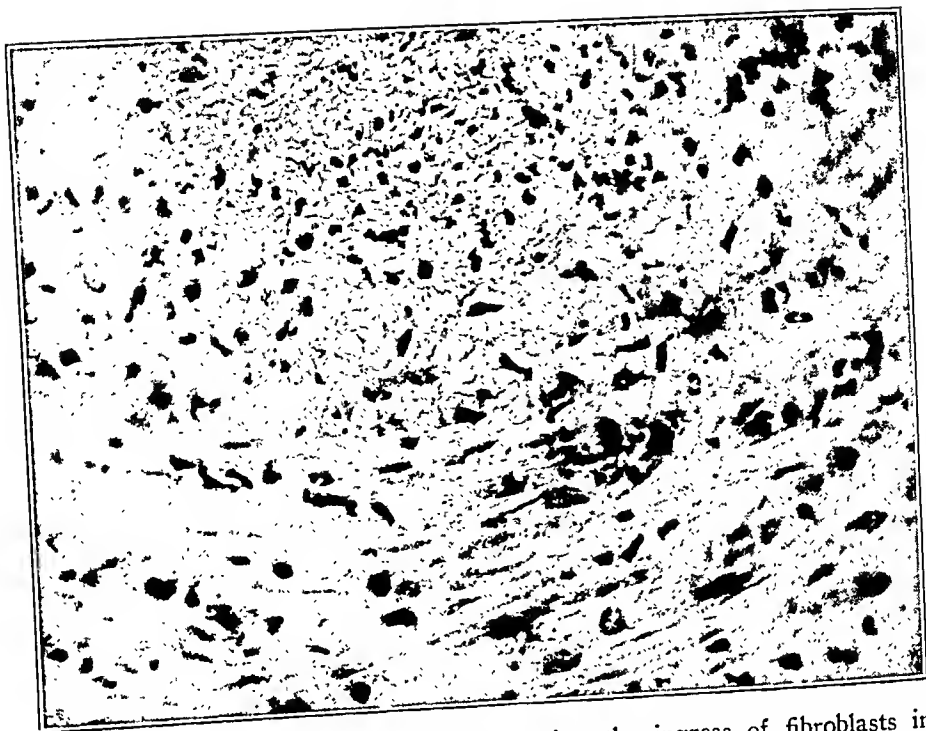


Fig. 6.—Photomicrograph of a vein showing the ingress of fibroblasts in a clot forty-eight hours after the intravenous injection of 3 per cent sodium gyno-cardate.

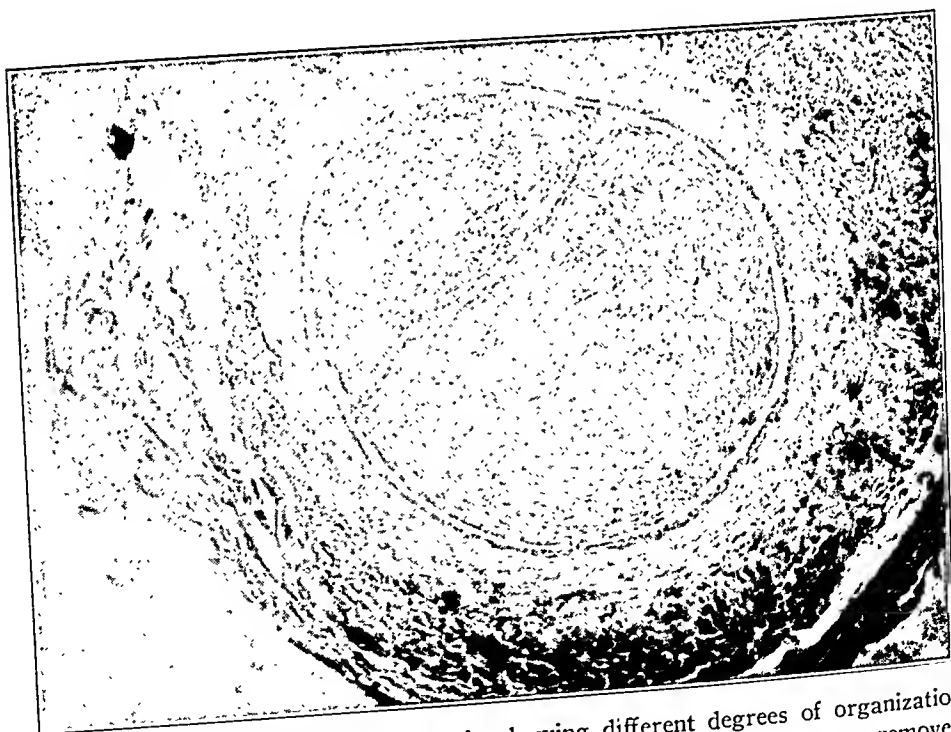


Fig. 7.—Photomicrograph of a vein showing different degrees of organization in the same lumen; one part is a secondary thrombus. The section was removed ten days after the injection of Searle's sodium morrhuate.



Fig. 8.—Photomicrograph of a vein showing organization of a thrombus practically complete fourteen days after the intravenous injection of 3 per cent sodium gynocardate.



Fig. 9.—Photomicrograph of a vein showing coagulation necrosis of the media, destruction of the intima and internal elastic lamina twenty-four hours after the injection of Searle's sodium morrhuate.



TABLE 1.—Degree and Incidence of Changes in Lumen, Intima and Internal Elastic Lamina After Intravenous Injection of Nine Different Sclerosing Solutions

	Destruction					Vacuolation					Exposure of Nuclei					Thrombosis					Pro- lifer- ation	Pyk- nosis	Internal Elastic Lamina Destroyed						
	0- Total 25%	25- 50%	50- 75%	75- 100%	Total 25%	25- 50%	50- 75%	75- 100%	Total 25%	25- 50%	50- 75%	75- 100%	Total 25%	25- 50%	50- 75%	75- 100%	0- Total 25%	25- 50%	50- 75%	75- 100%									
Sodium morrhuate, 5% (Searle's)	71.4	0	0	0	71.4	7.1	7.1	0	0	0	28.0	7.0	21.0	0	0	71.4	0	0	0	71.4	100.0	7.1	0	35.6	0	14.2	0	21.3	
Sodium gynoecardate, 5%	75.0	25.0	6.25	18.8	25.0	12.5	6.0	0	6.0	0	56.3	18.8	25.0	12.5	0	50.0	0	6.2	0	43.8	87.5	12.5	25.0	18.8	0	6.0	0	12.5	
Sodium gynoecardate, 3%	56.2	6.2	0	0	50.0	0	0	0	0	0	50.0	25.0	25.0	0	0	50.0	0	0	0	50.0	100.0	0	0	31.3	0	12.5	0	18.8	
Sodium gynoecardate, 2%	43.7	0	6.2	0	37.5	12.5	0	0	6.2	6.2	56.2	12.5	43.7	0	0	43.7	0	0	6.2	37.5	100.0	6.2	6.2	12.5	0	0	12.5	0	0
Sodium hydnocarpate, 5%	37.5	0	0	0	37.5	25.0	25.0	0	0	0	62.5	37.5	25.0	0	0	37.5	0	0	0	37.5	100.0	0	0	31.3	0	18.8	0	12.5	
Sodium hydnocarpate, 3%	33.3	0	0	0	33.3	33.3	33.3	0	0	0	60.0	60.0	0	0	0	33.3	0	0	0	33.3	93.5	6.7	0	20.0	0	0	0	20.0	
Sodium hydnocarpate, 2%	18.7	6.2	12.5	0	0	31.2	18.7	6.2	6.2	6.2	100.0	43.7	56.2	0	0	12.5	6.2	6.2	0	100.0	25.0	43.7	6.2	6.2	0	0	0	0	
Sodium morrhuate, 10% (our own)	37.5	6.2	6.2	6.2	18.7	18.7	6.2	6.2	6.2	0	75.0	37.5	37.5	0	0	18.7	0	0	6.2	12.5	100.0	12.5	31.3	12.5	6.2	0	0	6.2	
Sodium morrhuate, 5% (our own)	26.7	0	6.7	0	20.0	13.3	6.7	0	6.7	0	73.4	33.3	33.3	6.7	0	33.3	0	0	0	33.3	100.0	6.7	20.0	13.3	6.7	6.7	0	0	

duced some injury to the internal elastic lamina in 31.3 per cent of the sections. Others of the sclerosing substances produced injury to the lamina in smaller percentages even to 2 per cent sodium hydncarpate, which produced injury to the lamina in the smallest number of sections (6.2 per cent).

#### CHANGES IN THE MEDIA

*Edema.*—This change was the most frequent one observed in the media. The highest percentage of edema (75 per cent) occurred in the veins into which 3 per cent sodium gynocardate and 3 per cent sodium hydncarpate were injected. The lowest percentage of edema of the media (36 per cent) occurred in vessels into which Searle's sodium morrhuate was injected. In the veins into which the latter substance was injected, however, we noted coagulation necrosis or complete destruction of the media in 42 per cent of the sections, and in these instances edema was absent.

Hemorrhage was found in the media more often (20 per cent) in the sections of veins into which 3 per cent sodium hydncarpate was injected than with any other substance. There was no hemorrhage in any of the sections of veins into which Searle's sodium morrhuate was injected. As has been stated previously, this substance produces a high percentage of a more profound change-coagulation necrosis. Sodium gynocardate (5 per cent), next to Searle's sodium morrhuate the most efficient thrombus-producing drug in our series, produced hemorrhage in the media in only 6.2 per cent of the veins into which it was injected.

*Leukocytic Infiltration.*—Leukocytic infiltration was found in the media in a small percentage of instances after the intravenous injection of each of the nine solutions studied by us. The leukocytes were usually not found in abundance. Sometimes, however, the infiltration was marked (fig. 10). Sodium hydncarpate, 5 per cent, gave the highest percentage of leukocytic infiltration in the media (31 per cent). When this change was found, thrombosis usually had occurred.

*Connective Tissue Proliferation.*—This change was not an immediate one. Fibroblasts were noted in the media in some instances in sections removed as early as forty-eight hours. There was marked variation in the percentage of connective tissue proliferation produced by the different substances in this series. The percentage varied from 6.7 in the instance of 2 per cent sodium hydncarpate to 62.5 for 5 per cent sodium gynocardate. The presence of connective tissue in excess in the media was noted in the vessels showing thrombi that had been present for some time and was more marked in the vessels showing organized thrombi. An increase of connective tissue in the media closely

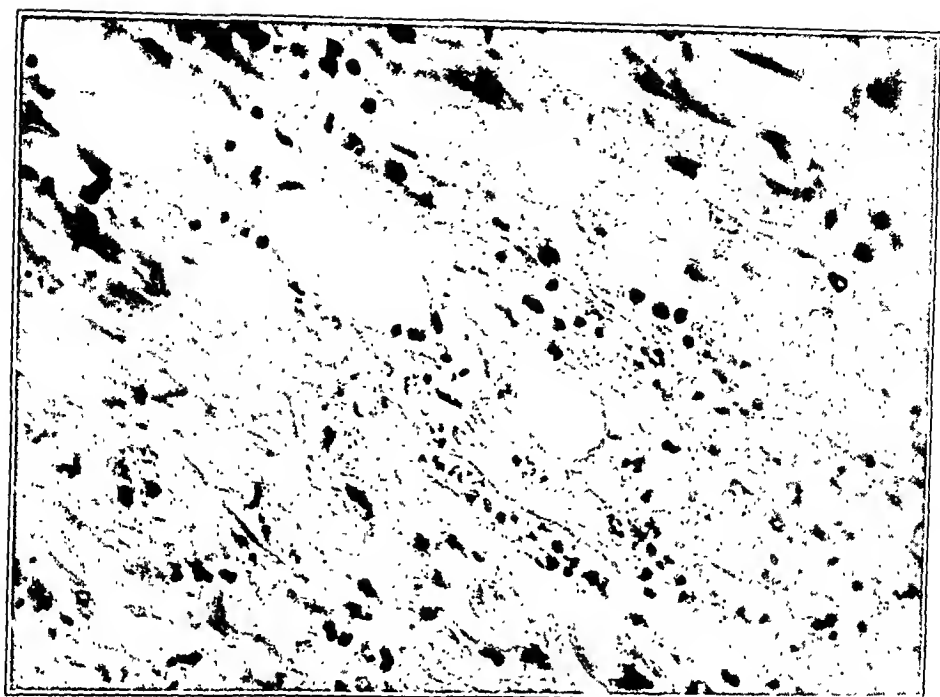


Fig. 10.—Photomicrograph of a vein showing leukocytic infiltration in the media forty-eight hours after the injection of Searle's sodium morrhuate.

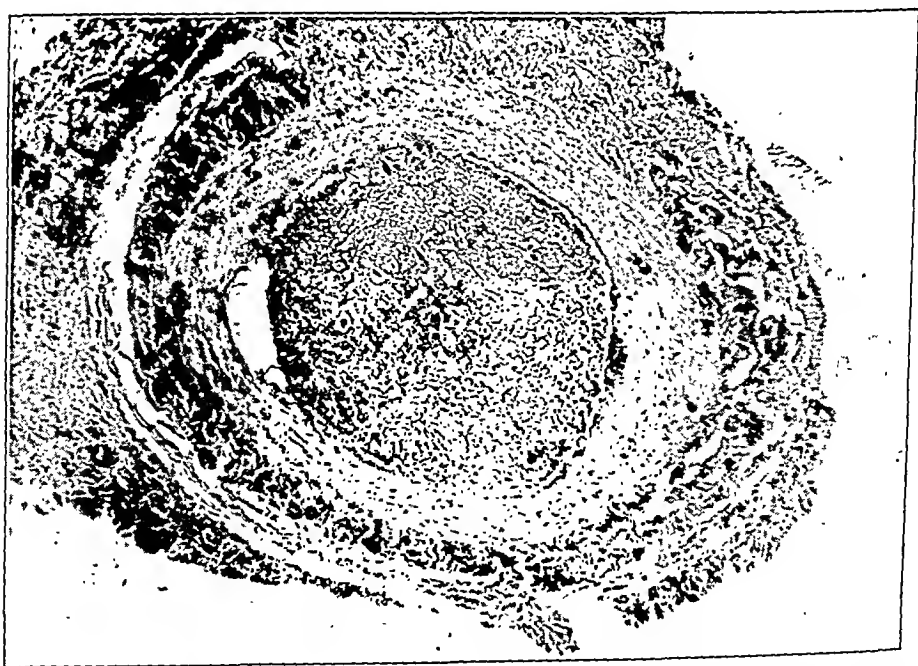


Fig. 11.—Photomicrograph of a vein showing an organized thrombus four weeks after the injection of Searle's sodium morrhuate.

paralleled the same change in the adventitia, as may be observed in tables 2 and 3. It is an indication of repair of injury to the media.

*New Blood Vessels in the Media.*—Normally in the peripheral vein of the dog there are no vessels in the media other than capillaries. When the vein is occluded by a thrombus, new vessels form in the media as well as through the clot in an attempt to reestablish a collateral circulation and also apparently in some instances in reaction to injury. The finding of new vessels in the media closely paralleled the finding of an occlusion of the lumen. In the instance of 5 per cent sodium gynocardate, 50 per cent of the sections showed new blood vessels in the media. Sections of vein removed after injecting our own sodium morrhuate (10 per cent) showed no new vessels in the media in any instance, but in only one section of those removed after twelve hours was the lumen occluded by a thrombus. Thus the appearance of new vessels in the media is an accompaniment of any thrombosis and together with the recanalization of the clot represents a reparative process in the reestablishment of circulation through new channels.

*Coagulation Necrosis.*—Searle's sodium morrhuate produced the most profound changes in the wall of the vein of all the substances we used. In 42.8 per cent of the sections of veins into which this substance had been injected there was evidence of injury of the muscle of the media to the extent even of presenting a glazed homogeneous, dull-staining, non-nucleated stratum of tissue, in which apparently the muscle cells had undergone necrosis (fig. 9). We did not determine the character of the reparative process which resulted in the recovery from this change in our sections, but the apparent necrosis did not seem to persist as it was not observed in sections removed after three days. Apparently the cells were injured but not completely destroyed, and were able to recover as there was no evidence of their being replaced by connective tissue in sections removed after longer periods. This change, therefore, cannot be considered an undesirable one because it does not interfere with normal processes of reaction to the sclerosing substance. On the other hand, it is probably of therapeutic value, because wherever coagulation necrosis in the media was found, a thrombus completely occluded the lumen of the vein. Although thrombosis occurred without coagulation necrosis, the latter was always accompanied by thrombosis. Coagulation necrosis also occurred in veins into which other substances had been injected; 5 per cent sodium hydriocarpate produced it in 18.8 per cent of the veins, but 5 per cent sodium gynocardate in no instance.

*Atrophy of the Muscle.*—In some instances in which there was an organized clot present the muscle cells seemed to be small and the nuclei elongated. This apparent atrophy was noticeable when a fibrous clot occluded the lumen and when there was evidence of an increase in the

TABLE 2.—Degree and Incidence of Changes in Media After Intravenous Injections of Nine Different Sclerosing Solutions

	Edema					Leukocytic Infiltration					Hemorrhage					Connective Tissue Proliferation					New Blood Vessels					Coagulation Necrosis	Muscle Atrophy
	0-25%	25-50%	50-75%	75-100%	75-100%	0-25%	25-50%	50-75%	75-100%	75-100%	0-25%	25-50%	50-75%	75-100%	75-100%	0-25%	25-50%	50-75%	75-100%	75-100%	Total 25-50%	50-75%	75-100%	75-100%	75-100%		
	Total 25-50%	50-75%	75-100%	75-100%	75-100%	Total 25-50%	50-75%	75-100%	75-100%	75-100%	Total 25-50%	50-75%	75-100%	75-100%	75-100%	Total 25-50%	50-75%	75-100%	75-100%	75-100%	Total 25-50%	50-75%	75-100%	75-100%	75-100%		
Sodium morrhuate, 5% (Searle)	71.4	35.6	21.3	14.2	0	14.2	7.1	7.1	0	0	0	0	0	0	0	21.3	14.2	7.1	0	0	7.1	0	7.1	0	0	14.2	
Sodium gynocardate, 5%	62.5	56.3	0	62.0	0	18.8	12.5	0	0	6.2	6.2	0	0	0	0	62.5	0	37.5	25.0	0	50.0	43.7	6.2	0	0	0	
Sodium gynocardate, 3%	87.5	75.0	12.5	0	0	25.0	0	25.0	0	0	18.8	0	6.3	6.3	6.3	31.3	25.0	6.3	0	0	18.8	6.3	6.3	6.3	0	6.4	18.2
Sodium gynocardate, 2%	68.7	56.2	6.2	6.2	0	12.5	0	6.2	6.2	0	12.5	0	6.2	6.2	0	25.0	12.5	12.5	0	0	12.5	6.2	6.2	0	0	12.5	6.2
Sodium hydnocarpate, 5%	75.0	50.0	25.0	0	0	31.1	12.2	18.8	0	0	0	0	0	0	0	12.5	12.5	0	0	0	12.5	6.2	6.2	0	0	18.8	12.5
Sodium hydnocarpate, 3%	86.6	73.3	0	13.4	0	26.7	13.4	0	13.4	0	20.0	0	20.0	0	0	13.4	13.4	0	0	0	13.4	13.4	0	0	0	0	13.4
Sodium hydnocarpate, 2%	82.3	62.5	18.8	0	0	6.2	6.2	0	0	0	0	0	0	0	0	31.2	18.7	12.5	0	0	0	0	0	0	0	0	0
Sodium morrhuate, 10% (our own)	93.5	68.8	25.0	0	0	12.2	0	12.2	0	0	0	0	0	0	0	12.2	0	12.2	0	0	0	0	0	0	0	0	0
Sodium morrhuate, 5% (our own)	59.7	53.0	6.7	0	0	6.7	0	6.7	0	0	6.7	6.7	0	0	0	6.7	6.7	0	0	0	6.7	6.7	0	0	0	6.7	0

TABLE 3 - Degree and Incidence of Changes in Arteritis After Intravenous Injections of Nine Different Sclerosing Solutions

TABLE 3 - Degree and Incidence of Changes in Adventitia After Intravenous Injections of Nine Different Sclerosing Solutions																														
	Edema					Hemorrhage					New Vessels					Leukocytic Infiltration					Hyperemia					Connective Tissue Proliferation				
	0-	25-	50-	75-		0-	25-	50-	75-		0-	25-	50-	75-		0-	25-	50-	75-		0-	25-	50-	75-		0-	25-	50-	75-	
	Total 25%	Total 50%	Total 75%	Total 100%		Total 25%	Total 50%	Total 75%	Total 100%		Total 25%	Total 50%	Total 75%	Total 100%		Total 25%	Total 50%	Total 75%	Total 100%		Total 25%	Total 50%	Total 75%	Total 100%		Total 25%	Total 50%	Total 75%	Total 100%	
Sodium morrhuate, 5% (Scaric)	100.0	50.0	12.0	7.1	0	35.6	7.1	14.2	0	7.1	0	7.1	0	42.8	21.3	14.2	7.1	0	50.0	7.1	28.5	14.2	0	7.1	0	7.1	0	7.1	0	0
Sodium gynocardate, 5%	50.0	50.0	0	0	0	0	0	0	0	43.8	43.8	0	0	25.0	12.5	12.5	0	0	62.6	43.8	18.8	0	0	50.0	50.0	0	0	0	0	0
Sodium gynocardate, 5%	50.0	50.0	0	0	0	6.5	6.5	0	0	25.0	0	25.0	0	25.0	0	12.5	12.5	0	56.2	12.5	43.7	0	0	37.5	37.5	0	0	0	0	0
Sodium gynocardate, 5%	87.5	37.5	37.5	12.5	0	0	0	0	0	0	0	0	0	18.7	6.2	12.5	0	0	68.7	62.5	6.2	0	0	6.2	0	6.2	0	0	0	0
Sodium gynocardate, 2%	56.2	25.0	25.0	0.2	0	0	0	0	0	0	0	0	0	25.0	18.8	6.2	0	0	50.0	18.8	25.0	0	6.2	25.0	25.0	0	0	0	0	0
Sodium hydnocarpate, 5%	75.0	50.0	25.0	0	0	6.2	0	6.2	0	37.5	31.3	6.2	0	26.7	13.4	13.4	0	0	26.7	20.0	6.7	0	0	6.7	6.7	0	0	0	0	0
Sodium hydnocarpate, 3%	86.0	73.5	13.4	0	0	0	0	0	0	13.4	13.4	0	0	6.2	0	6.2	0	0	31.2	25.0	6.2	0	0	6.2	6.2	0	0	0	0	0
Sodium hydnocarpate, 2%	75.0	75.0	0	0	0	12.5	0	12.5	0	6.2	6.2	0	0	6.2	0	6.2	0	0	62.5	25.0	37.5	0	0	18.8	6.7	12.2	0	0	0	0
Sodium morrhuate, 10% (our own)	100.0	31.3	62.5	6.7	0	6.1	0	6.7	0	6.7	0	6.7	0	40.0	20.0	20.0	0	0	53.1	26.7	26.7	0	0	0	0	0	0	0	0	0
Sodium morrhuate, 7% (our own)	100.0	73.3	26.6	0	0	26.7	0	20.0	6.7	6.7	0	6.7	0	40.0	20.0	20.0	0	0	53.1	26.7	26.7	0	0	0	0	0	0	0	0	0

interstitial connective tissue in the media. We interpret this as an expression of disuse. It was observed most commonly (18.2 per cent) in the sections of veins into which 3 per cent sodium gynocardate was injected. Only three sections of veins into which the latter drug was injected showed it. They were the veins removed after six, ten and fourteen days. These all had thrombi in the lumen, but no other veins removed later than six days after injection of this same substance showed thrombosis. Searle's sodium morrhuate produced atrophy of the muscle in 14.2 per cent of the sections. This is not a characteristic difference in the drugs but an indication of thrombosis that has occurred at some time prior to six days before removal, permitting sufficient time for atrophy to occur.

#### CHANGES IN THE ADVENTITIA

The changes in the adventitia resulting from the intravenous injection of sclerosing substances are chiefly those that might be expected in reaction to an irritant. In some instances they were marked; in others, mild, even though thrombosis might have occurred (table 3). Two changes (hemorrhage and leukocytic infiltration) were of especial significance, as they were almost invariably accompanied by thrombotic occlusion of the lumen. This was also evident in the investigation by Garside and one of us (A. O.).<sup>1</sup> Only occasionally were hemorrhage and leukocytic infiltration present without a thrombus.

Hemorrhage in the adventitia was observed most frequently (35.6 per cent) in the sections of veins into which Searle's sodium morrhuate was injected. It was not observed in any instance in the veins into which 5 per cent sodium gynocardate was injected. The sodium morrhuate, as was demonstrated in the media and the intima, produced more profound changes in the vessel than the 5 per cent sodium gynocardate, though the latter was scarcely less efficient in producing a thrombus.

Leukocytic infiltration of the adventitia occurred more frequently than hemorrhage. Leukocytic infiltration was found in 42.8 per cent of the veins into which Searle's sodium morrhuate was injected, and in 25 per cent of the veins into which sodium gynocardate (5 per cent) was injected. This change was seldom found after the third day, though it was observed in one instance as late as the twenty-first day.

Edema of the adventitia was frequently found. It was most marked in the early periods and decreased in the longer periods. It was present in all the veins into which Searle's sodium morrhuate was injected, though it was graded only as I (questionable) in 50 per cent of these instances. It was observed in half the veins into which 5 per cent sodium gynocardate was injected, and in no instance was it graded more than slight. All the other sclerosing substances showed edema of the adventitia in from 71 to 100 per cent of the sections.

Hyperemia of the vessels of the adventitia as manifested by dilatation and engorgement was present in sections removed at varying periods after injection. It was found in from 27 per cent (3 per cent sodium hydnocarpate) to 69 per cent (2 per cent sodium gynocardate) of the section. In some instances it represents reaction to inflammation, and in some instances undoubtedly an attempt to open the collateral blood channels.

New blood vessels and connective tissue proliferation in the adventitia are changes that closely parallel each other, as may be seen in table 3. This is to be expected. New vessels are attempts to form collateral circulation and were found in the vessels showing thrombosis that had been present forty-eight hours or longer. In three instances (our own 10 per cent sodium morrhuate, 5 per cent sodium hydnocarpate and 2 per cent sodium hydnocarpate) there was a suggestion of new vessel formation in the adventitia in forty-eight hours. This change was not observed to be sufficiently marked to grade it distinctly, however, before the fourth day (3 per cent sodium gynocardate). The percentage of new vessels in the media closely approximates the percentages of the same change in the adventitia, as may be observed in tables 2 and 3.

Connective tissue proliferation in the adventitia is an expression of repair. It was observed most commonly and most markedly in sections showing occlusion of the lumen by thrombosis.

Coagulation necrosis of cells of the adventitia was observed in a few instances (Searle's sodium morrhuate, once; 3 per cent sodium gynocardate, once; 10 per cent sodium morrhuate [our own], twice; 5 per cent sodium hydnocarpate, twice). This change was observed only in some parts of the adventitia of these vessels, and not throughout the entire coat. When it was present there was generally definite evidence of the presence of the sclerosing substance in the adventitia. In some of these instances we observed in the adventitia a brownish-yellow dull homogeneous substance that was undoubtedly the sclerosing substance. Probably in these instances there was some perivenous infiltration on the injected substance.

#### SUMMARY

Dogs were used as test animals to study the changes produced in veins by the intravenous injections of sclerosing substances and to determine the most efficient sclerosing solution. The method used was the same as that employed by Garside and one of us (A. O.),<sup>1</sup> and the results of the two studies are compared for thrombus-producing effectiveness. Nine solutions were investigated: 5, 3 and 2 per cent sodium gynocardate; 5, 3 and 2 per cent sodium hydnocarpate; 10 and 5 per cent sodium morrhuate (our own), and 5 per cent sodium morrhuate in benzyl alcohol (Searle). The results are given in percentages and



grades of changes found microscopically in sections of veins removed at sixteen time intervals from one-half hour to eight weeks. Searle's sodium morrhuate was the most efficient thrombus producer not only for our series, but also in a previous study<sup>1</sup> of twenty solutions. Sodium gynocardate, 5 per cent, was the next most efficient thrombus producer. Quinine and urea hydrochloride (from the earlier study) was only eighth in thrombus-producing effectiveness.

#### CONCLUSION

Experimental study on veins of dogs shows that sodium morrhuate (Searle) is the most efficient thrombus-producing solution of nine sclerosing solutions studied by us and twenty sclerosing solutions studied in a previous experiment.<sup>1</sup> Sodium gynocardate, 5 per cent, is the next most efficient intravenous sclerosing substance.

Destruction of the endothelium of a vein is the essential factor in the production of thrombus by a sclerosing agent.

# THORACOGENIC SCOLIOSIS

## INFLUENCE OF THORACIC DISEASE AND THORACIC OPERATIONS ON THE SPINE

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OMAHA

In recent years the more critical study of disease of the thorax and the extensive development of radical surgical treatment in suitable cases of pulmonary tuberculosis, bronchiectasis and similar conditions have directed attention but insufficient interest to the influence of thoracic disease and thoracic operations on the spinal column. This group of cases also provides an unusual opportunity for an investigation of the mechanics of the thoracic spine. To determine the mechanical factors involved in the production, frequency, clinical significance and prevention of thoracogenic curvatures, 518 patients with various forms of thoracic disease and 336 patients operated on for thoracic disease were studied; the results of the investigation form the basis of this report.

It should be emphasized at the outset that these curvatures only occasionally become so extensive that they give rise to symptoms or a deformity of clinical significance, and that the terms "curvature" and "scoliosis" as used throughout this article merely designate deviations from the normal and not necessarily deformity of the spine.

The normal thoracic spine is maintained in a state of static equilibrium by a balance of the opposing forces acting on the two sides of the vertebrae. These forces are exerted not only by the ribs, muscles and ligaments and other soft tissues of the thoracic wall but by pressures and stresses which arise within the thoracic cage (pleural, intrapleural and pulmonary forces). An appreciable imbalance of any one of these factors is likely to result in a deviation, the mechanisms of which will be discussed under their respective headings.

In general, the likelihood of a curvature and the extent to which the spine deviates under the influence of imbalance depend on: (1) age, for the younger the subject the more responsive is the spine to imbalance; (2) extent of imbalance, which is determined by such factors as the location and duration of the disease and the type of surgical attack, and (3) a certain unexplained compensatory mechanism (possibly muscle tone) whereby in 2 comparable cases apparently with equal

imbalance, slight or no deviation may develop in one patient, while an extensive deformity may develop in the other.

#### MECHANICAL ANALYSIS

*Rib Imbalance.*—The ribs are the principal agents for the support of the thoracic vertebrae by virtue of their rigidity not only as bony braces but also because of their service as instruments through which the forces exerted by the attached muscles and ligaments and the forces of intrathoracic pressures and stresses are transmitted to the vertebrae through their costovertebral articulations. Since the bony framework of the thorax is made up of a series of superimposed semirigid circular units, forces acting on one area are transmitted throughout the circumference of each unit. Normally each pair of ribs grips with pressure the vertebra with which it articulates. If this pressure is unequal on the two sides, or if it has been removed from one side by the extensive resection of ribs such as occurs in thoracoplastic operations (fig. 1 *A* and *B*), the unopposed ribs push the vertebrae toward the unsupported side, and a deviation results. A spine which was straight before operation will deviate with the convexity of the curve projecting into the side on which the operation was performed.

The degree to which this occurs depends on certain factors: (1) the number and length of the costal segments resected (fig. 1 *A* and *B*); resection of one small segment as in open drainage of an empyema cavity does not demonstrably influence spinal equilibrium; (2) the level of costal resections; as a rule much greater deviations result from the resection of the upper than from that of the lower ribs (fig. 1 *B* and *C*); (3) the proximity of the spine to the costal segments resected; as illustrated by figure 2, the closer to the spine the costal resection is carried, the greater is the deviation or the likelihood of a deviation. The removal of segments anterior to the angles of the ribs has slight or no influence on the spine. Apparently adequate support is maintained through the long residual posterior stumps and their important muscular attachments.

The curvatures which result from the imbalance produced by the resection of ribs may be designated as thoracoplasty scolioses (fig. 1 *A* and *B*). They usually involve only a short segment of the spine—as a rule, the upper thoracic segment—and they are often rather sharply angulated. With each successive stage of multistaged thoracoplasties the angle of the curvature is often slightly increased, and usually a more extensive segment of the spine becomes involved. When the stages progress downward from the upper to the lower ribs, the apex of the curve correspondingly moves downward slightly. Lateral deviations of considerable extent are accompanied by rotation of the vertebral



Fig. 1.—Thoracoplasty scoliosis illustrating rib imbalance: *A*, a short high dorsal dexter convex lateral curvature has developed in a previously straight spine as a result of the imbalance produced by the partial extrapleural posterolateral thoracoplasty. A large tuberculous cavernous lesion at the right apex was closed, and the disease arrested by the resection of long segments of the upper seven ribs. As in this case, most of the spinal deviations which develop with the extrapleural type of thoracoplasty in adults are so slight that they have little clinical importance. *B*, a retouched roentgenogram in a case of chronic empyema in which the patient was cured by thoracoplasty of the Schede type. Almost total costectomies of the third to the ninth ribs, inclusive, were done. A deforming curvature has been produced by the gross imbalance resulting not only from the extensive costal resections but from the wide excision of muscles and other soft tissues of the thoracic wall and of the restraining pleural scar. Before operation the spine deviated in the opposite direction. A pleural scoliosis therefore has been overcorrected and converted into a thoracoplasty scoliosis. *C*, in this case the spine deviated only slightly after a Schede thoracoplasty. The fourth to the ninth ribs, inclusive, were resected. The greater degree of curvature shown in *B* is probably caused by the more extensive resection of the upper ribs.

bodies and of the thoracic cage. As a result of this mechanical factor, the deformity resembles that of all other rotary scolioses, such as idiopathic and paralytic scoliosis, and differs from that of pleural scoliosis in which there is slight or no rotation of the vertebrae.

Contrary to the opinion of Nissen,<sup>1</sup> who stated that scoliosis due to a thoracoplasty develops several weeks after operation, it has been my observation that the deviations appear immediately or within a few days after the ribs have been removed. This fact has an important bearing on preventive therapy.

It is of interest that costal resections have been done for the purpose of correcting idiopathic scoliosis. Volkmann,<sup>2</sup> Hoffa,<sup>3</sup> Sauerbruch,<sup>4</sup>

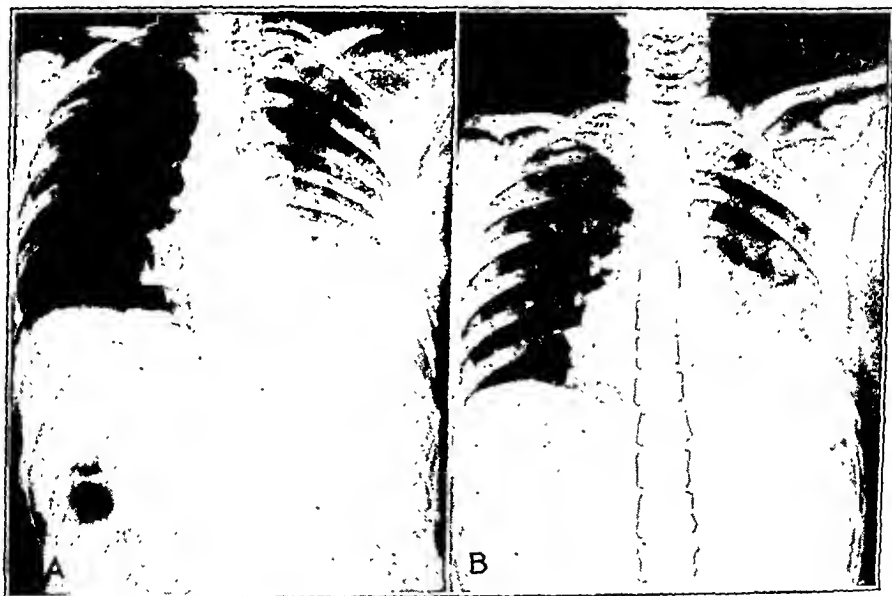


Fig. 2.—Rib imbalance, showing the influence of proximity to the spine: *A*, this patient had a pleural scoliosis associated with a mixed tuberculous empyema and osteomyelitis and chondritis of the overlying fifth, sixth and seventh ribs and costal cartilages. Resection of the anterior one third of these ribs and their cartilages did not alter the curvature. *B*, the same patient after a second operation, at which time the posterior segments of the same ribs were removed beyond their angles. The spine promptly straightened.

1. Nissen, R.: Mediastinalverlagerung bei postoperativer Skoliose und ihre praktische Bedeutung, München. med. Wchnschr. **75**:528, 1928.

2. Volkmann, R.: Rippenresection bei der Skoliose, Berl. klin. Wchnschr. **26**:1097, 1889.

3. Hoffa, A.: Operative Behandlung einer schweren Skoliose. Ztschr. f. orthop. Chir. **4**:402, 1895.

4. Sauerbruch, F.: Ueberlegungen zur operativen Behandlung schwerer Skoliosen, Arch. f. klin. Chir. **118**:550, 1921.

Loeffler,<sup>5</sup> Hoke,<sup>6</sup> Gaudier,<sup>7</sup> Casse,<sup>8</sup> Bade,<sup>9</sup> Lange<sup>10</sup> and others divided muscles and resected ribs on the side of the convexity or concavity or in both places, but their results have not encouraged a broad application of the principle.

*Muscle Imbalance.*—The influence of muscle imbalance in the production of spinal curvatures was pointed out by Leichtenstern<sup>11</sup> and is well illustrated by the paralytic scoliosis of anterior poliomyelitis and the spastic scoliosis of spastic hemiplegia. A mild spastic type of spinal curvature is observed often in cases of acute empyema (figs. 3 and 6B). As elsewhere in the body, nature attempts to immobilize and protect the acutely inflamed part by muscle spasm. The contracted muscles of the affected hemithorax and of the abdomen and neck on the same side narrow the intercostal spaces, draw the ribs downward and arch the spine with the concavity on the affected side. The spasm of the abdominal muscles may be so great that acute disease below the diaphragm is suspected.

The reverse type of deviation occurs as a result of the paralysis of a portion of the respiratory muscles produced by multiple intercostal neurectomy, an operation described by Alexander<sup>12</sup> and devised to give rest to a tuberculous lung. The second to the tenth intercostal nerves, inclusive, of one side are interrupted posteriorly to the rib angles.

To demonstrate the influence of muscle imbalance in the production of nonthoracogenic curvatures, Carey<sup>13</sup> devised an ingenious model of the vertebral column supported in equilibrium by the tension of rubber bands representing the principal opposing groups of muscles which act on the spine. By variously releasing the pull of certain bands he could

5. Loeffler, F.: Tenotomie der langen Rückenstrecker auf der Rippenbuckelseite bei Skoliosen, *Zentralbl. f. Chir.* **51**:825, 1924.

6. Hoke, M.: Study of a Case of Lateral Curvature of the Spine, *Am. J. Orthop. Surg.* **1**:168 (Nov.) 1903.

7. Gaudier, M. H.: Résection de la gibbosité costale comme adjuvant du traitement orthopédique de la scoliose, *Bull. et mém. Soc. de chir. de Paris* **46**: 1384, 1920.

8. Casse, J.: De la résection des côtes dans la scoliose, *Ann. Soc. belge de chir.* **4**:321, 1896.

9. Bade, P.: Rippenresektion bei schwerer Skoliose, *Zentralbl. f. Chir.* **30**: 1045, 1903.

10. Lange, F.: Das Ergebnis einer ausgedehnten Rippenresektion auf der konkaven Seite bei einer schweren Skoliose, *Ztschr. f. orthop. Chir.* **41**:207, 1921.

11. Leichtenstern, quoted by Rey.<sup>21</sup>

12. Alexander, J.: Phrenicectomy and Intercostal Neurectomy for Pulmonary Tuberculosis, *Ann. Int. Med.* **4**:348 (Oct.) 1930.

13. Carey, E. J.: Scoliosis: Etiology, Pathogenesis and Prevention of Experimental Rotary Lateral Curvature, *J. A. M. A.* **98**:104 (Jan. 9) 1932.

produce curvatures with slight or great vertebral rotation and with deviation laterally toward or away from the side which had been released.

Arnd<sup>14</sup> produced curvatures in animals by resecting the erector spinae group of muscles of one side.

It would appear, however, that muscle imbalance plays a minor part in the production of thoracogenic curvatures. In all cases that I have observed the curvatures which presumably were produced solely by muscle imbalance were of minor degree and importance.

*Intrathoracic Imbalance.*—Unbalanced forces arising within the thorax may act directly on the spine. Contracting scar tissue, with



Fig. 3.—Muscle imbalance in a case of spastic scoliosis: The protective muscle spasm associated with an acute empyema in a child of 2 years has drawn the costal cage downward and narrowed the intercostal spaces. These factors have deviated the spine with the concavity on the side of the empyema.

anchorage to the thoracic wall laterally as a fixed point and to the movable spine mesially, may draw the vertebral bodies in the direction of the fixed point. Usually, however, the force is transmitted to the spine through the ribs.

For the sake of clarity, intrathoracic imbalance may be divided into three groups: pleural, intrapleural and pulmonary.

*Pleural Imbalance; Pleural Scoliosis:* The literature refers to this type of scoliosis as empyema scoliosis. I use the term "pleural scoliosis"

14. Arnd, J.: Experimentelle Beiträge zur Lehre der Skoliose, Arch. f. Orthop. u. Unfall-Chir. 1:1, 1903.

because it describes more accurately the anatomic relationship and because the curvatures are often produced by pleural disease other than empyema. The pleural scar resulting from chronic pleuritis from any cause, such as a simple serous tuberculous effusion or tuberculous or nontuberculous empyema, contracts gradually and through adherence to the ribs pulls them centripetally. Since the ribs, like bucket handles, can pivot only at their extremities (the vertebral articulations posteriorly and the cartilages anteriorly) and inscribe arcs as they are drawn mesialward, they also move downward. This force is transmitted to the vertebral bodies through their costovertebral articulations, traction being exerted on the uppermost thoracic vertebrae by the upper ribs, which are pulled downward, and pressure being exerted on the lower ones, especially on those at the apex of the curve. The result is a spinal deviation with the convexity of the curve projecting into the healthy side, directed reversely to that produced by thoracoplasty.

It is of interest that this present day concept of unilateral stress exerted on the spine by the pleural scar was first advanced in 1827 by Delpeck,<sup>15</sup> to whom has been credited the earliest recorded recognition of the influence of thoracic disease on the spine. Walther,<sup>16</sup> Drachter,<sup>17</sup> Laennec,<sup>18</sup> Ziemssen<sup>19</sup> and Gaugele<sup>20</sup> stated the belief that the unbalanced respiratory function of the two sides which results from a pleural effusion and the atelectatic lung is an important factor in deviating the spine. Gaugele<sup>20</sup> suggested that negative intrapleural pressures may retract the thoracic wall in cases in which an effusion is rapidly absorbed. Rey<sup>21</sup> stated that in certain instances the weight of the fluid causes the spine to deviate with the convexity on the affected side in order to shift the center of balance and thereby gain equilibrium. Obviously this explanation applies only to spines bearing superincumbent weight which produces a curve directed reversely to that which is almost invariably observed.

15. Delpeck, J.: Ueber die Empyema, Abhandl. d. Akad. d. Wissensch., Chir. de Montpellier 1:3, 1827.

16. Walther, H.: Ueber die empyematische Skoliose, Ztschr. f. orthop. Chir. 26:401, 1910.

17. Drachter, R.: Bedeutung der Interkostalmuskelatrophie beim Raumausgleich im Thorax und der Begriff der Lungenstützfunktion, München. med. Wchnschr. 66:485, 1919.

18. Laennec, R.: Traité de l'auscultation médiate et des maladies des poumons et du cœur, Paris, J. C. Chaude, 1826.

19. Ziemssen, H.: Pleuritis und Pneumonie im Kindesalter, Berlin, Hirschwald, 1862.

20. Gaugele, K.: Die postpleuritische Skoliose und ihre Verhütung, München. med. Wchnschr. 66:442, 1919.

21. Rey, J.: Die praktische Bedeutung der postpleuritischen Skoliose im Kindesalter, Arch. f. Kinderh. 72:261, 1922.



The nature of the etiology of pleural scoliosis makes it a distinct clinical entity. It differs from all of the other types in that there is no or slight rotation of the vertebral bodies. This disobedience to the well recognized physical law (stressed by Lovett<sup>22</sup>) of the dissipation of part of the bending force of rods into the production of rotation or twisting is due to the immobilization of the ribs in their retracted positions. The vertebrae cannot rotate against the resisting pressure exerted on them by the ribs, which are rigidly fixed by the pleural scar. This scar in certain instances undoubtedly exerts force directly on the verte-

TABLE 1.—*Comparative Measurements of Thoracic Circumference in Five Consecutive Cases of Empyema with Scoliosis*

Patient	Type of Empyema	Age	Side of Empyema	From Midsternum	To Spinous Process	Hemithorax, Inches	
						Right	Left
C. T. ....	Acute	2	Left	2d rib	5th spinous process	9	8
				4th rib	7th spinous process	9½	8
				Tip of ensiform process	12th spinous process	9½	9½
K. D. ....	Acute	7	Left	2d rib	5th spinous process	12½	11½
				4th rib	7th spinous process	12¾	11½
				Tip of ensiform process	12th spinous process	12½	12½
J. K. ....	Chronic	22	Right	2d rib	5th spinous process	14¾	17½
				4th rib	7th spinous process	14¾	17¾
				Tip of ensiform process	12th spinous process	17¾	19½
J. B. ....	Chronic	24	Left	2d rib	5th spinous process	16½	18¾
				4th rib	7th spinous process	17	14
				Tip of ensiform process	12th spinous process	17	14¾
D. C. ....	Chronic	14	Right	2d rib	5th spinous process	12¼	14½
				4th rib	7th spinous process	12½	15¼
				Tip of ensiform process	12th spinous process	12¾	15

The maximum difference in the circumference of the two sides was 3 inches (7.6 cm.). Greater reductions in expansion occurred in the cases of chronic than in the cases of acute empyema. Von Kölliker<sup>23</sup> and Apert (Bull. Soc. de pédiat. de Paris 10:277, 1908) reported cases with slightly greater differences in the two sides.

bral bodies, which helps to prevent rotation and usually also fixes the mediastinum to the spine so that it deviates with the spine.

The retraction of the thoracic wall by scar tissue restricts the respiratory excursions and greatly reduces the volume capacity of the affected hemithorax. Comparative measurements of the circumference of the two halves of the thorax in 5 cases are compiled in table 1.

The influence of the pathogenesis of pleural scoliosis on the clinical picture which it produces is brought out effectively by comparing it with that of idiopathic scoliosis, as is presented in table 2, the drawings of figure 4 and the roentgenograms of figure 5 *A* and *B*.

22. Lovett, R.: The Element of Torsion in Lateral Curvature of the Spine, Am. J. Orthop. Surg. 149:353, 1903.

Intrapleural Imbalance: If the mediastinum is fixed so that it cannot shift to compensate for changes of intrapleural pressures on the two sides, unequal pressures can be maintained within the pleural cavities, and this imbalance may make itself felt on the spine through the medium of the thoracic wall and may result in a spinal deviation. In 3 of 102

TABLE 2.—Comparison of Deformities\*

Pleural Scoliosis	Idiopathic Scoliosis
<ol style="list-style-type: none"> <li>1. On the side of the concavity               <ol style="list-style-type: none"> <li>a. Increased downward inclination of the ribs; pulled downward and mesialward by pleural scar</li> <li>b. Intercostal spaces narrowed; ribs contact or overlap and fuse</li> <li>c. Thoracic wall (costal arches) flattened anteriorly and posteriorly</li> <li>d. As a result of the retraction of the ribs, hemithorax smaller than that on the opposite or convex side; the circumference from <math>1\frac{3}{4}</math> to 3 inches (3.5 to 7.62 cm.) smaller in five cases measured (table 1)</li> <li>e. Lung on this side relaxed and atelectatic</li> </ol> </li> <li>2. On the side of the convexity               <ol style="list-style-type: none"> <li>a. No posterior bulge of thoracic wall because there is no rotation deformity</li> <li>b. Shoulder high but scapula not prominent</li> </ol> </li> <li>3. Either no or only slight rotation and structural change of vertebral bodies†</li> <li>4. Curves usually rigid and often short and sharply angulated</li> <li>5. Often compensatory curvatures do not develop until the patient sits up and the spine bears weight</li> <li>6. Mediastinum usually deviates with the spine, to which it is fixed by scar tissue</li> <li>7. Reduction of vital capacity proportional to deformity (Flagstad and Kollman: J. Bone &amp; Joint Surg. 10:724, 1928)</li> </ol>	<ol style="list-style-type: none"> <li>1. On the side of the concavity               <ol style="list-style-type: none"> <li>a. Abnormally horizontal position of ribs; since the ribs rotate with the vertebra toward the side of convexity their arched shapes cause them to lift upward</li> <li>b. Intercostal spaces unchanged or only slightly narrowed</li> <li>c. Thoracic wall (costal arches) flattened posteriorly but bulged anteriorly, owing to vertebral rotation</li> <li>d. As ribs rotate upward and outward this hemithorax becomes larger than that of the opposite or the convex side</li> <li>e. Lung on this side partially emphysematous and partially atelectatic</li> </ol> </li> <li>2. On the side of the convexity               <ol style="list-style-type: none"> <li>a. Thoracic wall (costal arches) flattened anteriorly and bulged posteriorly at apex of curve, owing to rotation of vertebrae</li> <li>b. Shoulder high and scapula prominent</li> </ol> </li> <li>3. Always rotation and often great; usually structural changes (wedging)</li> <li>4. Frequently not rigid and often long and gently arched</li> <li>5. Patients are ambulatory, so compensatory curvatures frequently develop simultaneously with the primary curves</li> <li>6. Mediastinum does not deviate; it is free and maintains its normal position</li> <li>7. Same</li> </ol>

\* Compare with figures 4 and 5.

† Walther<sup>16</sup> investigated pleurogenic scoliotic spines and reported that: 1. Rotation of the vertebrae is slight or absent. 2. Only slight wedge formation of vertebral bodies occurs, but often there is a pronounced concave compression of the intervertebral disks. 3. The transverse processes present changes due to torsion.

cases of acute empyema there were extremely massive effusions which displaced the mediastinum far into the healthy side and as a result produced marked respiratory embarrassment. In these 3 cases the spine deviated with the convexity pointing toward the side on which the empyema occurred, the reverse of the direction of the curvatures observed in all of the other cases of acute empyema. They differed also in that the intercostal spaces were distinctly wider than normal. Two theoretical explanations are possible: 1. The mobile mediastinum may

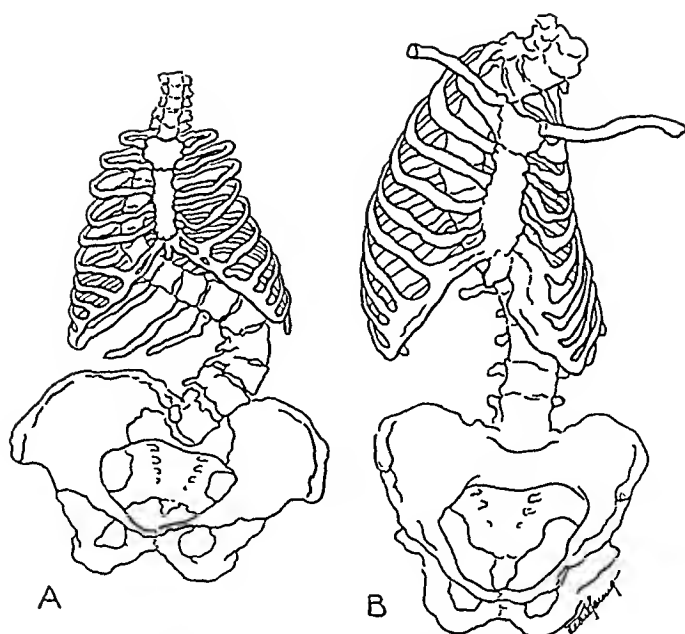


Fig. 4.—Diagrammatic drawings illustrating table 2, for a comparative analysis of rotary and nonrotary scoliosis. To the left is illustrated the rotation deformity of the thorax of idiopathic scoliosis, which typifies the rotary type of scoliosis. The drawing to the right represents the deformity of pleural scoliosis which uniquely is a nonrotary type of curvature (table 2).



Fig. 5.—Roentgenograms in a case of (A) idiopathic scoliosis and (B) pleural scoliosis. Compare with figure 4 and table 2. Note that the mediastinum did not deviate with the spine in A but did deviate in B.

have been displaced by the massive effusion until its elastic recoil permitted an increase of the intrapleural pressure on the affected side sufficient to widen the intercostal spaces and deviate the spine in the direction opposite to that produced by the traction of muscle spasm. 2. It is possible that a voluntary effort was made by the patient to minimize the mediastinal displacement, and consequently the respiratory embarrassment, by increasing the capacity of the affected hemithorax by widening the intercostal spaces and deviating the spine in a favorable direction. The roentgenograms in 1 of these cases have been reproduced (fig. 6).

Occasionally, as is illustrated in figure 7, a pneumothorax maintained for a considerable length of time, with high or moderately positive pres-

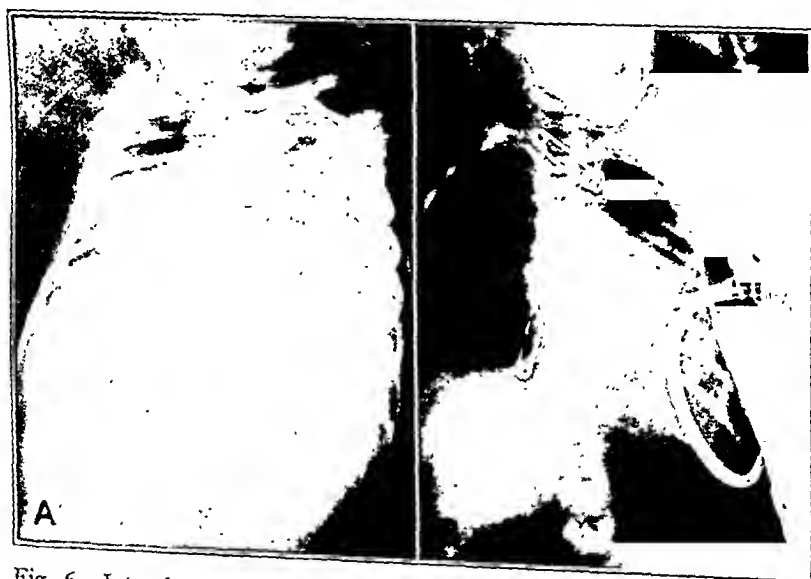


Fig. 6.—Intrapleural imbalance: *A*, an acute empyema of the left side with a massive effusion which has displaced the mediastinum far into the right side and diminished the available aerating lung to such an extent that the patient was cyanotic and dyspneic. Note the widening of the intercostal spaces on the left side and the spinal deviation with the convexity to the left. *B*, the same patient after drainage was established. Note the narrowing of the left intercostal spaces and the reversal of the spinal curvature, which is now of the spastic type characteristic of acute empyema.

tures against a fixed mediastinum, will produce the same deformity as that described earlier, namely, a widening of the intercostal spaces and a spinal deviation with the convexity on the side of the pneumothorax.

If the mediastinum has normal mobility it offers less resistance than do the thoracic cage and spine to unbalanced intrathoracic forces on the two sides, and it will shift into either side from its normal midline

position and within certain limits will prevent an imbalance. It compensates for unequal pressures on the two sides by increasing the volume of one hemithorax at the expense of the other in an endeavor to maintain the normal physiologic, less than atmospheric, intrapleural pressures.

**Intrapulmonary Imbalance:** The forces exerted by the lungs on the thoracic wall and transmitted through it to the spine are not infrequently unbalanced by such conditions as massive pulmonary atelectasis and emphysema and by extensive pulmonary fibrosis (fig. 8A). Again, the influence of these conditions on the spine depends to a large measure on the ability of the mediastinum alone to compensate for the unilateral or unbalanced stress.

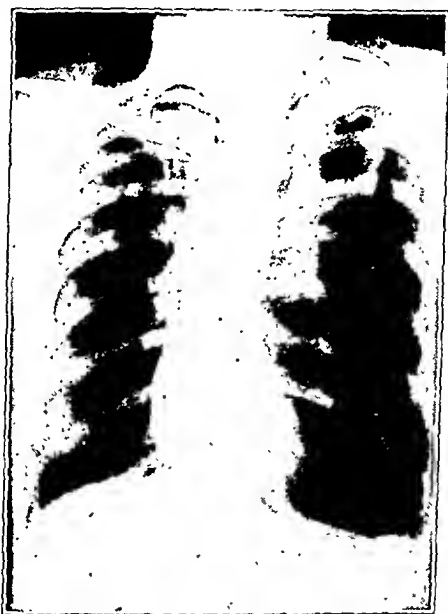


Fig. 7.—Intrapleural imbalance: A case of pulmonary tuberculosis with a large open cavity at the left apex which artificial pneumothorax therapy has failed to close because of adhesions which suspend the lung to the lateral thoracic wall. As a result of maintaining the intrapleural pressure considerably above atmospheric, the intercostal spaces of that side have been widened and the spine deviated with the convexity toward the side of the pneumothorax.

Pulmonary disease which has produced extensive parenchymal fibrosis frequently has extended to the pleurae and produced a pleuritis which often fixes the lung to all or any part of its bony and mediastinal encasement. Consequently, as the scar tissue in the lung contracts, stress is exerted on these attachments with three possible results: 1. If the mediastinum is mobile, it is pulled into the affected hemithorax, and since this pull takes place slowly and gradually, the mediastinum has time to stretch and may therefore shift to a remarkable degree (fig.

8 B). 2. The pleural scar may produce a pleural scoliosis which diminishes the volume of the affected hemithorax and gives relaxation to the fibrosing lung. 3. If the lung is anchored to the vertebral bodies mesially and to the thoracic wall laterally, the force of contracture of the fibrosing lung not infrequently will pull the less resistant point of anchorage, the vertebral bodies, toward the fixed point, the ribs of the lateral thoracic wall. Since these ribs pass obliquely upward posteriorly and articulate with vertebrae above those to which the lung is anchored, the pull on these ribs is transmitted to the vertebrae in the form of pressure which pushes them in the direction opposite to those at the apex of the curve. In other words, the vertebrae and ribs in the direct line of force



Fig. 8.—Pulmonary imbalance: *A*, a roentgenogram of a patient with far advanced pulmonary tuberculosis; a large right apical cavity and extensive parenchymal fibrosis are present. With the lung anchored to the thoracic wall laterally and to the vertebral bodies mesially by the scar of an associated pleuritis, the shrinkage of the fibrotic lung has pulled the movable vertebral bodies toward the fixed point, the lateral thoracic wall. *B*, in this case of pulmonary tuberculosis, the contracture of the fibrotic and atelectatic right lung has drawn the mediastinal structures into the right hemithorax. Note the complete dexter cardia, dexter displacement of the trachea and the compensatory emphysema of the left lung. In the absence of fixation to the spine, the mediastinum and left lung shifted to the right to balance the force of the shrinkage of scar tissue. The spine was therefore uninfluenced.

at the apex of the curve are pulled on directly, while the vertebrae immediately above the apex are acted on indirectly through the ribs. Figure 8 *A* illustrates the result of the action of these forces.

## CLINICAL CLASSIFICATIONS

In the following classifications, the curvatures have been grouped according to degree: (1) slight, or of no clinical significance; (2) moderate, a deviation of clinical importance without appreciable deformity, and (3) severe, or extensive curvatures with deformity. Obviously this grouping is merely relative.

*Acute Empyema; Spastic Scoliosis.*—In this investigation all cases of empyema of less than three months' duration have been classified arbitrarily as acute, and those of longer duration as chronic (fig. 3).

TABLE 3.—*Acute Nontuberculous Empyema; the Influence of Age on the Incidence and the Degree of Scoliosis*

Age, Years	Right Empyema Sinister Convex Scoliosis (Degree)				Left Empyema Dexter Convex Scoliosis (Degree)				Reversed Curves	Total Cases
	Number Cases	None	Slight	Mod- erate	Number Cases	None	Slight	Mod- erate		
0-10	23 (43.4%)	12 (52.1%)	7 (30.5%)	2 (8.7%)	17 (34.7%)	8 (47%)	6 (35.3%)	3 (17.6%)	2	40
10-20	11 (20.7%)	6 (54.5%)	5 (45.5%)	0	12 (24.5%)	6 (50%)	5 (41.6%)	0	1	23
20-30	10 (19%)	7 (10%)	3 (30%)	0	5 (10.2%)	3 (60%)	1 (20%)	1 (20%)	0	15
30+	9 (16.8%)	7 (77.7%)	1 (11.1%)	0	15 (30.6%)	9 (60%)	6 (40%)	0	1	24
Totals	53	32 (60%)	16 (30.1%)	2 (3.7%)	49	26 (53%)	18 (36.7%)	4 (8.1%)	4	102

TABLE 4.—*Acute Nontuberculous Empyema; the Influence of the Duration of the Disease on the Incidence and the Degree of Scoliosis*

Duration of Disease	Degree of Scoliosis			Total
	None	Slight	Moderate	
0 to 4 weeks.....	43 (62.3%)	23 (33.3%)	3 (4.3%)	69
4 to 12 weeks.....	11 (39.3%)	15 (53.5%)	2 (7.1%)	28
Totals.....	54 (55%)	38 (39%)	5 (6%)	97

One hundred and two cases of acute empyema were studied (tables 3 and 4). Forty-four presented spinal deviation, in 38 (86.4 per cent) of slight and in 6 (13.6 per cent) of moderate degree.

Empyema of the left side predominated slightly and was associated with a slightly greater incidence of spinal deviations. In all but 4 cases the spine deviated with the concavity on the affected side. Three of the 4 cases manifested extremely massive effusions; they were discussed in an earlier paragraph (fig. 6). In the other case there was a pre-existing rachitic scoliosis. The influence of age on the incidence and degree of deviation was definite but not striking. In 40 patients with ages ranging below 10 years there was an incidence of 50 per cent as

compared with 30 per cent in 24 patients over 30 years of age. Likewise the duration of the disease increased the incidence of scoliosis from 37 per cent in cases observed within four weeks of the onset of the empyema to 60 per cent in those of longer duration.

Since the curvatures of acute empyema are produced mainly by muscle spasm, they usually correct themselves completely unless the disease progresses to chronicity.

*Chronic Empyema; Pleural Scoliosis.*—Since all of the pleural scolioses, regardless of etiology, present a typical clinical picture, comment

TABLE 5.—*Chronic Nontuberculous Empyema; the Influence of Age on the Incidence and the Degree of Scoliosis*

Age, Years	Right Empyema Sinister Convex Scoliosis (Degree)				Left Empyema Dexter Convex Scoliosis (Degree)				Right and Left, Totals
	Number Cases	None	Slight	Mod- erate	Number Cases	None	Slight	Mod- erate	
0 to 10.....	10 (23.3%)	3 (30%)	3 (30%)	4 (40%)	6 (10.1%)	1 (16.6%)	2 (33.3%)	3 (50%)	16
10 to 20.....	16 (37.2%)	4 (25%)	5 (31.2%)	7 (44.8%)	17 (28.8%)	4 (23.5%)	9 (53%)	4 (23.5%)	33
20 to 30.....	3 (7%)	2 (66.6%)	1 (33.3%)	0	14 (23.7%)	4 (28.5%)	6 (43%)	4 (28.5%)	17
30+.....	14 (32.5%)	9 (64.3%)	5 (35.7%)	0	22 (37.2%)	11 (50%)	7 (31.5%)	4 (18.5%)	36
Totals.....	43	18 (41.8%)	14 (32.5%)	11 (25.7%)	59	20 (34%)	24 (42.3%)	14 (23.7%)	102

TABLE 6.—*Chronic Nontuberculous Empyema; the Influence of the Duration of the Disease on the Incidence and the Degree of Scoliosis*

Duration of Disease	Degree of Scoliosis			Total
	None	Slight	Moderate	
3 to 6 months.....	13 (56.5%)	9 (39.1%)	1 (4.3%)	23
6 to 12 months.....	8 (36.3%)	8 (36.3%)	6 (27.3%)	22
Over 12 months.....	16 (30.7%)	17 (32.7%)	19 (36.5%)	52
Totals.....	37 (38%)	34 (35%)	26 (27%)	97

will be inclusive of the entire group of 146 cases of chronic empyema (figs. 5 B and 9 A). Of these, 102 (70 per cent) of the patients were nontuberculous (tables 5 and 6), and 44 (30 per cent) were tuberculous, the infections being pure and mixed (tables 7 and 8). Of the total group, curvatures developed in 95 (65.8 per cent); they were of slight degree in 61, moderate in 37 and severe in 2 per cent.

In all except 2 of the cases the spine arched with the concavity toward the affected side, and in these cases (tuberculous empyema) the reverse type of the curvature could be explained by mechanical factors incident to extensive pulmonary and pleural disease of the contralateral side.

As in the series of cases of acute empyema, there was a predominance of left-sided lesions (83 to 63), and the percentage incidence of scoliosis



was slightly greater in the cases of left-sided empyema. It is possible that the right lobe of the liver may resist the downward movement of the ribs on that side.

Rey<sup>21</sup> reported a study of 31 cases in which the patients were cured of chronic empyema by simple drainage. In 27 cases there were demonstrable scolioses, but in 2 of these cases the curvatures antedated

TABLE 7.—*Tuberculous Empyema; the Influence of Age on the Incidence and the Degree of Scoliosis*

Age, Years	Empyema on the Right Side Sinister Convex Scoliosis (Degree)					Empyema on the Left Side Dexter Convex Scoliosis (Degree)					Right and Left, Total
	Number Cases	None	Slight	Moderate	Moderately Severe	Number Cases	None	Slight	Moderate	Moderately Severe	
0-10	3 (15%)	0	2 (66.6%)	0	1 (33.3%)	2 (8.3%)	0	1 (50%)	0	1 (50%)	5
10-20	1 (5%)	0	1 (100%)	0	0	4 (16.6%)	2 (50%)	2 (50%)	0	0	5
20-30	10 (50%)	5 (50%)	2 (20%)	3 (30%)	0	9 (37.5%)	2 (22.2%)	5 (55.5%)	2 (22.2%)	0	19
30+	6 (30%)	2 (33.3%)	3 (50%)	0	0	9 (37.5%)	3 (33.3%)	4 (44.4%)	2 (22.2%)	0	15
Total	20	7 (35%)	8 (40%)	3 (15%)	1 (5%)	24	7 (29.3%)	12 (50%)	4 (16.6%)	1 (4.1%)	44

TABLE 8.—*Tuberculous Empyema; the Influence of the Duration of the Disease on the Incidence and the Degree of Scoliosis*

Duration of Disease	Degree of Scoliosis				Total
	None	Slight	Moderate	Moderately Severe	
0 to 4 weeks.....	4 (50%)	4 (50%)	0	0	8
4 to 12 weeks.....	3 (37.5%)	3 (37.5%)	2 (25%)	0	8
12 to 24 weeks.....	0	8 (66.6%)	3 (33.3%)	0	12
24 to 52 weeks.....	4 (40%)	5 (50%)	1 (10%)	0	10
More than 52 weeks.....	7 (43.8%)	1 (6.2%)	6 (37.5%)	2 (12.5%)	16
Total.....	18 (33.3%)	21 (38.8%)	12 (24%)	2 (3.7%)	54

the onset of the empyema. In all except 1 of the cases the spine deviated with the concavity on the affected side.

In the groups of acute and chronic empyema the incidence of scoliosis and the extent of deviation varied roughly in inverse proportion to the age of the patients and in direct proportion to the duration of the disease. The ratio in certain groups was almost 2:1 (tables 3 to 8).

Pulmonary Disease.—One hundred and eighty patients who had pulmonary tuberculosis uncomplicated by pleural effusions and who were not treated surgically were studied. The disease in most instances involved both lungs. In 32 (17.8 per cent) of the cases there was slight

but definite deviation of the spine, with the convexity of the curve directed to the side which was the more extensively diseased in 43.2 per cent and in the reverse direction in 56.8 per cent. Without exception, the deviations could be explained by one of the mechanical factors previously discussed: (1) extensive parenchymatous fibrosis with retraction of the thoracic wall, mediastinum and vertebral bodies; (2) extensive pleural involvement and the production of a pleural scoliosis, and (3) massive atelectasis in the presence of a fixed mediastinum (only 1 case).

Of the 48 consecutive cases of pulmonary abscess which were studied, 6 (12.5 per cent) were complicated by empyema, and in 4 (66 per cent) of these typical pleural scolioses had developed. In only 3 (7.1 per cent)



Fig. 9.—The influence of thoracic operations on the spine: *A*, a tuberculous empyema of two years' duration in a child of 4 years has been productive of a moderately severe pleural scoliosis. *B*, the same patient two weeks after completion of a Schede thoracoplasty. Note the correction of the pleural scoliosis by the imbalance produced by the operation.

of the remaining 42 uncomplicated cases was there evidence of spinal deviation, and in each of these there was evidence of retraction from extensive pulmonary fibrosis.

Forty-two unselected cases of bronchiectasis were studied; 5 (11 per cent) were complicated by empyema, and typical pleural scolioses had developed. Of the 37 uncomplicated cases, only 1 presented a deviation. In this case (fig. 11 *A* and *B*) the curvature could be explained only by assuming a certain instability which later permitted the spine to collapse completely as a result of a lobectomy.

From these data it is apparent that pulmonary disease seldom produces an imbalance capable of deviating the spine unless there is extensive pulmonary fibrosis or involvement of the pleura.

#### INFLUENCE OF THORACIC OPERATIONS

Although various surgical operations on the thorax may disturb the static equilibrium of the spine, only those involving extensive resection of the ribs, and the lobectomies produce deformities of clinical importance.



Fig. 10.—The influence of thoracic operations on the spine: *A*, the roentgenogram of a patient with multiple pulmonary abscesses of the lobes of the left lung complicated by empyema. Pleural scoliosis has developed. *B*, the same patient after completion of a total posterolateral thoracoplasty. A high dorsal thoracoplasty scoliosis has been superimposed on the pleural scoliosis, giving rise to a double or S-shaped curve.

*Thoracoplasty.*—A study of 131 patients treated by thoracoplasty showed that the contour of the spine is always altered, but that this alteration is influenced by the preoperative contour.

1. A spine which was straight previous to operation almost invariably deviated with the convexity toward the side on which operation was performed. This occurred in 59 (45 per cent) of the cases (fig. 1).



Fig. 11.—The influence of thoracic operations on the spine: *A*, roentgenogram of a patient with bronchiectasis of the right lower lobe, which has been filled with iodized poppy-seed oil, 40 per cent. Note the slight sinister convex scoliosis. *B*, the same patient three years after total excision of the right lower lobe. The spine has reversed its curvature and completely collapsed into the side on which operation occurred. Note the rotation of the vertebrae and the deformity of the thoracic wall caused by the rotation. *C*, photograph of the same patient illustrating the characteristic deformity of rotary scoliosis.

2. If it deviated with the convexity toward that side before operation the curvature was greatly exaggerated by thoracoplasty. This occurred in 21 cases (16 per cent).

3. If, however, it curved in the opposite direction (preoperative pleural scoliosis), the deviation was partially or completely corrected. This occurred in 12 (9 per cent) of the cases (fig. 9). Often the contour was overcorrected; this occurred in 39 (29 per cent) of the cases (fig. 11). In 5 cases a double or S-shaped curve developed, composed of a thoracoplasty curvature superimposed on a preexisting pleural scoliosis (fig. 10 *A* and *B*).

TABLE 9.—*The Influence of Extrapleural Thoracoplasty on the Spinal Column in One Hundred and One Cases*

	Degree	Preoperative Scoliosis			Postoperative Scoliosis		
		Right	Left	Straight Spine	Right	Left	Straight Spine
A. Right thoracoplasties (41 cases)	Slight.....	9	4	22	6	0	1
	Moderate....	0	2	0	32	0	0
	Totals.....	9	6	22	38	0	1
B. Left thoracoplasties (60 cases)	Slight.....	11	7	31	0	13	1
	Moderate....	4	..	..	0	46	..
	Totals.....	15	7	31	0	59	1

TABLE 10.—*The Fate of Curvatures of Pleural Scoliosis in One Hundred and Five Patients with Subacute and Chronic Emphysema Treated by Thoracoplasty and Simple Drainage*

Simple Drainage (69 Cases)			Thoracoplasty (36 Cases)		
No change in curvature (26 cases)	Progression of curvature (26 cases)	Correction of curvature (17 cases)	Partial correction (2 cases)	Complete correction (8 cases)	Overcorrection (26 cases)
					Double or S-shaped curves Thoracoplasty curvatures superimposed on a pleural scoliosis (5 cases)

Of the 131 thoracoplasties, 101 were extrapleural and were carried out in the treatment of pulmonary tuberculosis. The remaining 30 operations were Schede thoracoplasties for empyema; the intercostal soft tissues and much of the parietal pleural scar were excised as well as the ribs. As a result of this additional resection (soft tissues and restraining parietal pleura), the Schede type of operation (fig. 1 *B*) as a rule produced greater imbalance and greater alteration of spinal contour than did the extrapleural type.

Before operation, in the group of 101 patients treated by extrapleural thoracoplasty there were 53 with straight spines and 48 with curvatures. Only 2 of the 101 patients had straight spines after operation, which effected complete correction of the preoperative curvatures (table 9).

Of the 30 patients treated by the Schede type of thoracoplasty, 5 had straight spines, 10 had slight deviations, and 8 had moderate curvatures before operation. After operation there were 7 patients with straight spines representing corrections of previous curvatures and 7 with slight, 9 with moderate and 2 with moderately severe overcorrections. Double curvatures developed in 3 cases, the original preoperative deviations remaining unchanged except for the overcorrection of the upper dorsal segments.

The morphologic characteristics of thoracoplasty scoliosis have been considered under the topic of rib imbalance.

*Simple Drainage of Empyema Cavities.*—The rapid obliteration of the cavities in acute empyema by early adequate dependent drainage prevents extensive fibrosis of the pleurae and consequently prevents pleural scoliosis. In 43 cases of acute empyema with adequate follow-up data in which early rapid closure of the pleural cavity occurred, there were 17 in which correction of a spastic type of curvature took place soon after the establishment of the drainage, 26 in which no deviation developed and only 2 in which slight curvatures persisted after a complete cure of the empyema (table 10).

Pleural scoliosis frequently does not develop until weeks or months after the onset of the empyema, and not infrequently the curvatures progress gradually over a period of many months. Von Kölliker<sup>23</sup> and Hedblom<sup>24</sup> have observed a progression of curvatures for as long as two years. Latent progressive curvatures developed in 26 of 62 cases of chronic empyema in which adequate data were obtainable for a period of three months or more.

*Operations Which Produce Imbalance of Muscle Function (Phrenicectomy, Scalenotomy and Intercostal Neurectomy).*—A study of 50 consecutive cases of pulmonary tuberculosis in adults who were treated by phrenicectomy alone failed to reveal a deviation of the spine which could be attributed to the paralysis of half the diaphragm produced by this operation. An interval of at least three months after operation elapsed between comparative observations.

Harrenstein<sup>25</sup> reported the occurrence of scoliosis in 2 infants with unilateral diaphragmatic paralysis resulting from injury at birth. He attributed the scoliosis to the diaphragmatic paralysis. In both cases

23. von Kölliker, T.: Zur Verhütung und Behandlung der pleuritischen und empyematischen Skoliose, *Deutsche med. Wchnschr.* 30:634, 1904.

24. Hedblom, C. A.: Deformity of the Thorax Secondary to Pleural or Pulmonary Disease, *J. A. M. A.* 94:162 (Jan. 18) 1930.

25. Harrenstein, R. J.: Das Entstehen von Skoliose infolge einseitiger Zwerchfellähmung, *Ztschr. f. orthop. Chir.* 56:101, 1932.

there were also extensive injuries to the brachial plexus, with paralysis of all of the muscles of the arm, which offers a more likely explanation of the scoliosis.

By unilateral phrenicectomy Marconi<sup>26</sup> produced scoliosis in young rabbits in which rickets had been simultaneously produced experimentally by the administration of a strontium preparation. The convexity of the primary curvature was always on the paralyzed side.

In three patients treated by scaleniotomy (division of the three scalene muscles) no change occurred in the contour of the spine.

Four cases in which multiple intercostal neurectomy had been done were studied. In 3 of them slight but definite deviations of the spine developed after operation, and in each instance the convexity of the curve pointed toward the side on which operation had been performed.

*Lobectomy and Drainage of Pulmonary Abscesses.*—Following total extirpation of the lower lobe of a lung in 11 consecutive cases of bronchiectasis, a thoracoplasty type of scoliosis developed in 9 instances. The curvatures were slight in 3, moderate in 5 and severe in 1 case. The last case is illustrated in figure 11. In this case only was there a curvature before operation, and this curvature was slight.

Since the incidence and extent of the curvatures which develop after lobectomy are greater than reasonably could be explained by the imbalance produced by the costal resections necessary for the operative approach, it would appear that other factors contribute to the imbalance. The large space which is left after the lobe has been removed is obliterated by the remaining lobes, the mediastinum, the diaphragm and the thoracic wall, which are drawn into the space by contracting fibrous tissue. It is probable that the vertebral bodies are pulled laterally toward the thoracic wall and take part in obliterating this space.

Surgical drainage of pulmonary abscesses in 15 cases was productive of spinal deviations in only 5 cases; 4 deviations were slight, and 1 was moderate. Before operation there was a curvature (slight) in only 1 case. Drainage of the lower lobe was done in 2 of these cases; curvature of slight degree developed in 1 case and of moderate degree in the other.

*Miscellaneous Thoracic Operations; Induced Pneumothorax and Extrapleural Pneumolysis.*—Occasionally an artificial pneumothorax may cause the spine to deviate slightly. Since the intrapleural pressures and other circumstances related to pneumothorax therapy are so inconstant, no statistical data were collected.

Twenty-two patients who were treated by unilateral extrapleural paraffin pneumolysis were studied. Slight deviations developed in 14

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26. Marconi, S.: Alterazioni rachidie sperimentali da tossici, Chir. d. org. di movimento **13**:585 (July) 1929.

of the series. The convexity of the curve was directed toward the side of operation in 10, and toward the opposite side in 4 cases.

#### PREVENTION AND TREATMENT OF PLEURAL SCOLIOSIS

Although the principal interest in most of the spinal deviations incident to thoracic disease and thoracic operations is academic, a certain small minority progress to a stage of deformity. The deformities occur only in certain cases of pleural scoliosis, occasionally subsequent to extensive costal resections and lobectomies, and only in children and young adults.

Extensive deformity from any cause produces not only disfigurement of great concern to the patient, but also much impairment of cardiac and respiratory functions and often subjective symptoms such as pain and ease of fatigue. The restriction of respiratory excursions greatly reduces the capacity of pulmonary ventilation. Disturbed anatomic relations of the heart and great vessels which impair their functional efficiency and evidence of interference with the return flow of the pulmonary circulation with chronic passive congestion of the lungs have been observed frequently at necropsy (Eckhardt<sup>27</sup>). These factors not only limit the patient's activities but also diminish his ability to combat any severe illness successfully. Pneumonia is a frequent cause of death.

As pointed out previously, the spinal deviations associated with acute nontuberculous empyema usually correct themselves when the empyema cavity is obliterated promptly. Deformities develop with the chronicity of the disease, which, with few exceptions, reflects improper treatment. The first objective in the prevention of pleural scoliosis is therefore the early closure of empyema cavities by early, adequate and dependent drainage. Von Kölliker<sup>23</sup> stated that the development of scoliosis is best prevented by the rapid healing of the disease. No scoliosis developed in any of his cases in which drainage was done early by rib resection.

In pure tuberculous effusions rapid closure of pleural cavities may be effected only by repeated thoracenteses, because drainage is contraindicated, but drainage is applicable to many tuberculous effusions which are secondarily infected by pyogenic micro-organisms.

In all cases with pleural effusions, regardless of the etiology, a constant effort should be made to hold the spine in alinement or slightly overcorrected during the major portion of each twenty-four hours, not only during the period of active treatment, but also for several months after the pleural cavity has been obliterated in order to prevent deform-

27. Eckhardt, H.: *Untersuchungen über die Lage von Brust und Baueingeweiden bei hochgradiger Kyphoskoliose*, *Ztschr. f. orthop. Chir.* 48:125, 1927.



ity from latent contracture of the pleural scar. With the exception of infants and uncooperative children, this can be accomplished in most patients by posture; the patients lie on their affected sides, and if this simple procedure does not deviate the spine in the direction of overcorrection sufficiently to counteract the tendency to a pleural scoliosis, it may be supplemented by wedging, which is described under the topic "postural wedge compression." In ambulatory patients it may be carried out during rest hours during the day and at night.

Gaugele<sup>20</sup> advised the use of an Abbott plaster jacket for the prevention, as well as the correction, of pleural scoliosis. The jacket is provided with a window for the care of drainage tubes and dressings. The Abbott treatment of all forms of scoliosis has in recent years been abandoned, and its use in the presence of active disease of the pleural cavity would be objectionable because of the interference with respiration and the proper supervision of the empyema, the lesion of primary importance.

As pointed out previously, the extensive costal and pleural resections of extrapleural and Schede thoracoplasties, when done primarily to obliterate chronic residual pleural cavities, may partially or completely correct mild or even deforming pleural scolioses. Not infrequently an overcorrection is produced, and this is treated as a simple thoracoplasty scoliosis.

These same principles have been utilized by Hedblom,<sup>24</sup> Lilienthal,<sup>28</sup> Sauerbruch,<sup>29</sup> Gurd<sup>30</sup> and others in the treatment of residual pleural scoliosis in patients who have been cured of pleural or pulmonary disease. These surgeons have reported marked correction of curvatures by removal of ribs and pleural scars and by pulmonary decortication.

#### PREVENTION AND TREATMENT OF THORACOPLASTY SCOLIOSIS

Although the vertebral column deviates or sags into the unsupported side of the chest after the extensive costal resections of a posterolateral thoracoplasty, it is sufficiently plastic to permit considerable molding and correction by force until it becomes fixed from four to eight weeks after operation by the regenerated ribs, organized fibrous tissue and reinserted muscles. If correction is maintained during this reparative period, permanent curvatures will be minimized and often prevented. If, however, the periosteum has been destroyed or excised (as it is in a Schede thoracoplasty) the resected costal segments are not replaced, and the

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28. Lilienthal, H.: *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 1925, vol. 1.

29. Sauerbruch, F.: *Chirurgie der Brustorgane*, Berlin, Julius Springer, 1920, vol. 1.

30. Gurd, F. B.: *Scoliosis Accompanying Chronic Infected Open Pneumothorax*, *Arch. Surg.* 5:366 (Sept.) 1922.

spine is permanently deprived of much of its support on the side on which operation has been performed. In many instances, however, this lack of support may compensate for the previous imbalance from the pleural scar and merely correct a preoperative pleural scoliosis. The postoperative prophylactic maintenance of correction by postural wedging in these cases is beneficial but less effective than in the cases in which extrapleural thoracoplasty is done.

#### COMPRESSION BY A POSTURAL WEDGE

The spine can be controlled and held in a corrected or overcorrected position most simply and most effectively by posture alone or by compression by a postural wedge. In the latter procedure, illustrated in figure 12, the patient lies on the diseased side or the side on which

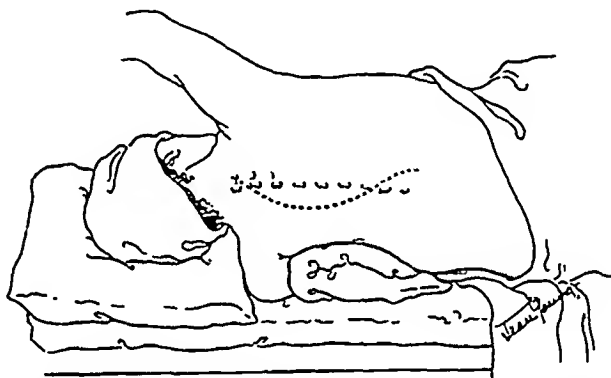


Fig. 12.—Postural wedge compression (Bisgard, J. D.: *J. Thoracic Surg.* 3:99 [Oct.] 1933): The patient lies on the diseased side or the side on which operation was performed, over a pillow which has been rolled in the direction of its long axis and placed at right angles to the axis of the body. By placing this fulcrum properly, the spine can be wedged in the direction desired. To correct and prevent pleural scoliosis, the fulcrum is placed high in the axilla, wedging the spine in the direction of overcorrection. To correct a thoracoplasty scoliosis the wedge is placed slightly more distal, that is, directly opposite or slightly caudal to the apex of the curve. The change of spinal contour which can be brought about by this procedure is illustrated diagrammatically by the straight alinement of the spinous processes. The curved, broken line illustrates the position of the spine of a thoracoplasty scoliosis before wedging.

operation has been performed, on a soft compression wedge, such as a pillow which is rolled in the direction of the long axis and placed at right angles to the axis of the body. If this fulcrum is placed properly, the weight of the body wedges the spine in the direction desired. In cases of developed or potential pleural scoliosis, the wedge is placed high in the axilla of the diseased side (with the arm completely abducted and the head elevated) so that the entire thoracic spine is deviated in

the reverse direction, the direction of overcorrection. To correct and prevent thoracoplasty scoliosis, it is placed exactly opposite or slightly caudal to the apex of the curve, thus applying pressure on the spine at a lower level. The correction which can be obtained by postural wedging is illustrated in figure 13.

This procedure not only is the simplest and most effective method of controlling the vertebral column, but also has the added advantage of contributing compression and immobilization to the thoracic wall and rest to the diseased lung or pleurae. Also, it does not interfere with the free respiratory excursions and pulmonary ventilation of the



Fig. 13.—Postural wedge compression: *A*, a roentgenogram of a thoracoplasty scoliosis taken with the patient sitting upright. The first stage operation had been done three weeks, and the second stage operation one week, previously. *B*, the same patient; this roentgenogram was taken during postural wedging, with the patient lying on the side on which operation occurred. In comparing the two roentgenograms, note that almost complete correction of the curvature has been obtained by wedging. The arrows in both roentgenograms outline an open pulmonary cavity which is partially concealed by the vertebral shadows in *B*, but with the vertebrae wedged into straight alinement in *C*, its entire circumference is clearly visualized. This use of postural wedging to gain increased roentgenologic visualization of the compressed lung after thoracoplasty has been reported elsewhere (Bisgard, J. D.: *J. Thoracic Surg.* 3:99 [Oct.] 1933).

healthy side. Except for these reasons the curvatures of pleural scoliosis could be wedged equally or more effectively with the patient lying on the unaffected side, with the fulcrum placed at the apex of the curve.

To illustrate this point and to indicate other circumstances in which postural wedging may be used, a case is cited.

Recently a child with extensive third degree burns of the left half of the trunk was treated by postural wedging. As a result of protective spasm and scar contracture, a moderately severe dexter convex curvature had developed. The curvature was promptly corrected with the patient lying on the uninvolved side over a rolled pillow, and the correction was constantly maintained until the burned areas had become completely epithelized with the aid of skin grafting. The child was examined one month after weight bearing had been resumed, and the spine was straight.

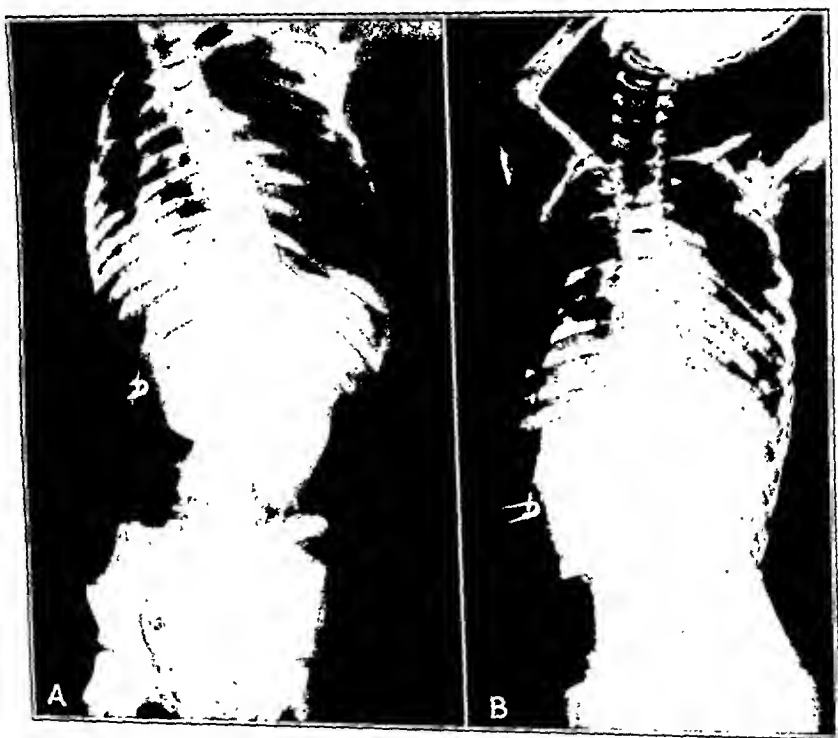


Fig. 14.—A child of 7 years with chronic empyema and an early pleural scoliosis: *A*, roentgenogram taken with the patient standing, and *B*, roentgenogram taken with the patient lying and undergoing postural wedging.

Young children may be held in position for postural wedging in a plaster bed which is molded to the body with the patient lying on the side. The side walls should be high enough to prevent the child from rolling out of this position.

With cooperation from the patient, postural wedge compression may be started immediately or a day or two after operation and within a few days may be maintained almost continuously.

For a few cases in which well developed deformities occur and for cases in which the curvatures are definitely progressing, the following

procedures have been recommended by many orthopedic surgeons: (1) corrective gymnastic and breathing exercises; (2) supportive body braces and jackets; (3) longitudinal traction on the head and pelvis, and (4) osteosynthesis of the spine after correction with a Risser turnbuckle cast.

When established, the curvatures of pleural and thoracoplasty scolioses are more resistant to correction than all other types, such as the paralytic and the idiopathic. When they are progressive, their progression likewise is much more difficult to prevent and usually continues despite the support of a body jacket or brace. Likewise, stretching and corrective exercises neither correct nor alter the course of progressive scoliosis. In most instances these curvatures can be controlled only by the internal fixation obtained by fusion of the entire spinal segment which constitutes the primary curve.

#### SUMMARY

1. A study of the influence on the spinal column of thoracic disease in 518 cases and of the surgical operative treatment of thoracic disease in 336 cases is reported. While lateral deviations of the thoracic spine had developed in a large percentage of cases in both groups in only 11 cases were the deviations great enough to give rise to a deformity of major clinical importance. Deforming curvatures occurred in only a few cases with extensive chronic pleuritis and in an occasional case in which successful treatment necessitated an extensive Schede thoracoplasty or lobectomy. It is significant that these deformities occurred only in children and young adults (less than 20 years of age).

2. Certain observations and deductions of academic interest are presented. With the etiology of many thoracogenic curvatures definitely known and capable of analysis, an unusual opportunity is given to study the mechanics of the thoracic spine. The various types of curvatures and the mechanism by which they are produced are described. This mechanism is presented on the basis of an imbalance of the opposing forces acting on the vertebrae.

3. All curvatures may be divided into two principal groups: (a) Rotary scoliosis. In thoracoplasty, as in most, if not all, types of scoliosis with the exception of pleural scolioses, the force of torsion associated with lateral deviation causes the vertebral bodies to rotate into the side of convexity. (b) Nonrotary or pleural scoliosis. All curvatures produced by the scar of chronic pleuritis are designated as pleural scolioses. This type of curvature is unique in respect to the absence of rotation of the vertebral bodies.

4. Methods of prevention and treatment of thoracogenic curvatures are discussed. Most pleural scolioses may be prevented by the early cure

of the pleural disease and by constant maintenance of correction or overcorrection of the spine by postural wedging. Also, many instances of thoracoplasty scolioses may be prevented by constantly wedging the spine straight until it becomes fixed.

For the control and treatment of certain severe and progressive curvatures, internal fixation by fusion of the vertebral column is recommended. Every patient less than 20 years of age who has had chronic infection of the pleural cavity or has been treated by extensive thoracoplastic operations should be observed frequently for at least a year, and if the curvature shows a tendency to progress despite conservative treatment, the spine should be fused to prevent the development of a severe deformity.

From this study and from clinical observations the author has been unable to discern any criterion by which one may prognosticate in an individual case the likelihood or degree of development of thoracogenic curvatures.

# HEALING OF FRACTURES

## ITS INFLUENCE ON THE CHOICE OF METHODS OF TREATMENT

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For the last two decades the problem of bone formation in its various aspects has occupied the attention of many investigators. That phase of the question which deals with the mechanism of healing after fracture has been prominent in the field, and during this time quite new conceptions of the process have been evolved. From the purely academic aspect many points relative to the exact mechanism of the process are disputed. It may be considered that there is no unanimity of opinion on the following questions: (1) whether there exist in the human adult specific bone-forming cells—osteoblasts; (2) whether such cells can be evolved on demand, so to speak, by metaplasia of ordinary fibrillar connective tissue cells; (3) whether only certain connective tissue cells are capable of this transformation; (4) whether the cell itself plays any active part of a specific nature in the process; (5) whether there is formed in the process of ossification a specific preosseous substance or matrix, and if so, (6) whether, after it is calcified, it is possible to remove calcium therefrom without coincidentally removing the associated matrix; (7) whether the deposition of calcium in the tissue associated with the formation of bone, be it in a preosseous matrix or not, is the result of the activity of an enzyme or independent of it; (8) if an enzyme is involved, whether it is the product of local cellular activity, specific or otherwise, or of local death of cells, or whether it originates at some point remote from the site of the formation of bone and is brought to the scene of action by the blood stream. The bibliography covers the range of the investigations along these lines and reveals a tremendous diversity of opinion.

Disregarding for the purposes of this article the purely academic side of the question, and taking into consideration only the phases of the problem which can be of practical working value to the man who has to take care of fractures and promote their prompt and efficient healing, there can be gathered from the mass of conflicting findings and inter-

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Read before the Section on Orthopedic Surgery, at the Eighty-Fourth Annual Session of the American Medical Association, Milwaukee, June 16, 1933.

pretations thereof a number of observations which appear to have sufficiently substantial support to warrant clinical application in the treatment of fractures in the adult.

I shall first present the observations which are sufficiently well supported to be, if possible, clinically applied; next, a résumé of the main supportive evidence for these observations, and finally, my point of view as to the influence of these observations on the treatment of fractures in general and as to the special application of some of them to specific fractures.

#### A. OBSERVATIONS SUFFICIENTLY WELL SUPPORTED TO BE, IF POSSIBLE, CLINICALLY APPLIED

I. All fractures heal as do wounds elsewhere, unless there is a mechanical, chemical or anatomic bar to the healing. This healing, in common with that of wounds of the soft parts, takes place through the medium of new connective tissue known as granulation tissue. When referring to delayed union and nonunion after any fractures in which healing through granulation tissue has occurred, one in reality refers to a delay or failure in the process of calcium deposition in the healing connective tissue which is commonly designated as new bone formation.

II. Variations in the character and amount of the healing process in bone following fracture are dependent on factors limited to the region of the body involved, quite independent of the subject involved.

*Corollary 1.*—Slow union and nonunion are not influenced by the age (*per se*) of the patient, by his general state of health, by the presence of chronic general disease such as syphilis or cardiovascular or renal disease, by general wasting due to other causes, by general metabolic disturbances affecting either the general calcium and phosphorus metabolism (osteomalacia) or other phases of metabolism (diabetes) or by acute infectious disease.

*Corollary 2.*—Therapy designed to alter the patient's general metabolism, specifically to affect his general calcium or phosphorus metabolism or his general state of health, have no appreciable effect on the process of healing.

III. The four factors involved in the mechanism of the healing of fractures and capable of being clinically influenced are: (1) the local pathology; (2) the growth of granulation tissue; (3) an available local source of calcium for the ossification of the healing tissue, and (4) a proper biochemical status of the local tissue fluids throughout the healing process.

*Local Pathology.*—The items of importance under this factor are: (a) The amount of tissue necrosis. When massive, it destroys available sources for the growth of granulation tissue and under all circum-



stances it creates a  $p_H$  to the acid side (often markedly so) in the hematoma and tissue fluids about the site of the fracture. This  $p_H$  is of importance in the production of the local source of calcium and is the essential early stage of the biochemistry of the tissue fluid.

(b) The hematoma or blood effusion at and about the site of the fracture. This influences the growth of granulation tissue through its fibrin content and the possible persistence of its fluid content in situ, and also the establishment of a local source of calcium under proper conditions of  $p_H$  in the tissue fluid by acting essentially as a decalcifying fluid and, through adsorption affinity between calcium and its fibrin content, by holding the freed calcium in situ.

(c) The circulatory status of the part (including the lymphatic and tissue fluids) in the early and late stages of fracture healing. Its significance lies in its influence on the growth of granulation tissue, and on the establishment of and utilization of a local source of calcium through its influence on the  $p_H$  of the tissue fluids.

(d) Chemical and physical influences through their effect on the growth of granulation tissue and the biochemical status of the part. Under the former may be noted the therapeutic use of chemicals locally (disinfectants, etc.) and infection, and under the latter, the use of such agencies as roentgen rays and diathermy.

(e) The mechanical element, i. e., the interposition of living or dead material impermeable to the growth of granulation tissue between the fragments.

*Growth of Granulation Tissue.*—The items of importance under this factor are: (a) The amount of tissue necrosis in relation to the amount of healing tissue called for in replacement. All other factors being equal, the amount of callus produced is directly proportional to the amount of granulation tissue produced.

(b) The amount of tissue necrosis in its relation to the destruction of available sources for the growth of granulation tissue.

(c) The anatomic characteristics of the part in relation to the availability of sources for the growth of granulation tissue and accessory circulation.

(d) The amount of fluid persisting for a long period at the site of the fracture.

(e) Elements *d* and *e* mentioned under local pathology (chemical and physical influences and the mechanical element).

*Available Local Source of Calcium.*—The items of importance in the ossification of the healing tissues are: (a) The amount of bone necrosis.

(b) The density and degree of fragmentation of the necrotic bone.

(c) The influence of fibrin and collagen in fixing the calcium locally through chemical affinity.

(d) The biochemical status of the local tissue fluids.

*Proper Biochemical Status of the Local Tissue Fluids Throughout the Healing Process.*—This factor involves the necessity in the local tissue fluid of a  $p_H$  on the acid side in the early days following the fracture in connection with the establishment of a local source of available calcium for ossification of the healing tissue, and a reversion of the  $p_H$  of the local tissue fluid toward the alkaline side before the calcium made available can be to any extent deposited in the new tissue to form bone. The constituents normally involved in this phase of the process are the amount of tissue necrosis, the content of local living tissue cells, the degree of metabolic activity of the cells and the circulatory status (blood and lymph) of the part.

#### B. EVIDENCE SUPPORTING THE OBSERVATIONS LISTED UNDER A

I. Whether, as an academic question, there exists in the adult a specific osteoblast essential to new bone formation, whether any or certain connective tissue cells may under proper conditions be transformed through metaplasia into cells specifically concerned in new bone formation, i. e., become osteoblasts, or whether there is no need for the specific activity of any cell in the process—new or young connective tissue being the only necessity—it must be acknowledged that the actual formation of bone occurs only after undifferentiated connective tissue healing and by a transformation of that healing known as ossification. Regardless again of the academic discussion as to whether this transformation is effected with or without the formation of a preosseous matrix and as to whether the calcium deposition therein is the result of the activity of a ferment or independent of such an activity, it is to the transformation of ordinary wound healing into bone that the terms slow union, delayed union and nonunion refer. The only true nonunions—that is to say failures of healing—are those due to the mechanical, chemical, physical and anatomic causes discussed subsequently under III (factors involved in the healing of fractures).

II. The preponderance of evidence, clinical and experimental, supports this observation. In the absence of the local factors mentioned under I of section A and discussed under III of this section, which prevent even ordinary connective tissue healing, and interpreting the terms slow union, delayed union and nonunion to refer to variations in calcium deposition in the healing connective tissue, the following may be listed in support of observation II and its corollaries:

Certain regions of the body, even under apparently optimum conditions, are characterized by a slow average healing time and by fre-

quent occurrence of delayed union and nonunion in adults. The neck of the femur (subcapital or midcervical), the junction of the lower and middle thirds of the tibia, the scaphoid of the carpus (proximal half), the base of the fifth metatarsal and the junction of the lower and middle thirds of the humerus are characteristic regions.

In patients who have fractures in these regions and simultaneous fractures in regions not so characterized there is no perversion of healing in the latter, all other factors except location being equal.

The preponderance of evidence based on recorded observation and not on impression is against the influence of any of the factors listed under corollary 1. All the factors listed may influence mortality markedly. In a leg which has been edematous and secondarily fibrosed for a long time as a result of cardiac or renal disease the healing may be abnormally slow, but the cause is the local circulatory status and not the cardiac or renal disease. If the local circulatory status can be influenced, even by mechanical means, healing may be influenced, though the disease itself may go on to a fatal issue while the healing is progressing normally. Similarly it is true that older people are more subject to vascular and chronic cardiac or renal disease. The mortality is apt to be high following injury in these patients. But if the local circulatory status of the part involved by fracture is not irreparably compromised, the healing of a fracture is not affected, nor is it at all affected in a patient of any age if there is no impairment of the circulatory efficiency of the part.

The theory that the presence of syphilis is deterrent to the healing of a fracture has long been exploded. It is conceivable and probable that local vascular impairment, local necrosis and sclerosis of the bone from any cause may be factors interfering with the normal process.

The preponderance of clinical and experimental evidence on the calcium and phosphorus levels of the blood during the healing of a fracture is unquestionably to the effect that there is no correlation between variations in these levels and variations in the healing process. In keeping with this are the clinical findings in osteomalacia and rachitis, in which healing is normal or slightly more rapid than normal after fracture, although there exists an actual negative balance in the former and an acknowledged metabolic disturbance in the latter. In cases of fragilitas ossium the healing is also unaffected by the presence of the disease. The same is true of cases of fibrocystic disease per se. A case at the Presbyterian Hospital a few years ago furnished a striking example of the lack of correlation between the state of calcium metabolism and the healing of a fracture. A gastro-enterostomy had been performed four years previously for the relief of a supposed gastric ulcer. The patient was admitted several times for successive spontaneous fractures. Roentgen examination showed general osteoporosis.

The phosphorus and calcium levels of the blood remained constantly normal, though the patient showed a negative balance. Eventually death resulted from an embolus. An autopsy showed the supposed gastro-enterostomy to have been a triple anastomosis between the stomach, jejunum and transverse colon as the result of a gastrocolic fistula, so that most of the food passed directly from the stomach to the transverse colon. Under these conditions the intake of calcium was negligible, and the blood calcium was kept up by withdrawals from the skeletal system. Despite this situation all the fractures healed with profuse callus.

My personal observations and the recorded clinical observations of others offer no support for the suggestion that there is any material variation in the healing of a fracture in patients with general metabolic disturbances, such as diabetes, disease of the thyroid gland and similar conditions, which is referable to the disease in the absence of thoroughly adequate grounds for such variation at the site of the fracture.

Corollary 2 follows 1 as a logical sequence, and, in addition, is supported by the recorded literature and by my personal investigations and observations over a number of years.

III. The following factors are involved in the mechanism of fracture healing:

1. *Local Pathology.*—(a) Tissue necrosis. The primary healing following a fracture is always by a tissue indistinguishable from granulation tissue; this tissue can be, and often is, derived in large part from tissue entirely outside of the bony structures; in fact, following tissue necrosis in the soft parts quite distant from bone, the formation of bone occurs in numerous sites in the body following disease and injury and can be produced experimentally in granulation tissue without the introduction of any osseous elements. Massive necrosis of tissue affecting the sources for the growth of granulation tissue into and about the site of the fracture from osseous or soft part structures is obviously a bar to the primary healing, without which the subsequent healing of the bone is impossible. Necrosis of tissue is accompanied by autolysis and often by a marked change in  $p_H$  to the acid side in the tissue fluids. A  $p_H$  as low as 4.2 has been recorded. The local primary acidity over a period of days (for which tissue necrosis is partly responsible) has been definitely established after a fracture. The importance of this primary acidity of the tissue fluids and its rôle in the decalcification of the dead bone at the site of the fracture is discussed in more detail under factors 3 and 4.

(b) Hematoma or blood effusion at the site of the fracture. By animal experiment and observations on tissue cultures, the relationship between adequate formation of fibrin network and satisfactory growth of granulation tissue is made clear. The demonstrated early acid  $p_H$

of the fluid portion of the blood effusion is of significance as regards its effect on the  $p_H$  of tissue fluid and its rôle in making local calcium available and in utilizing it for deposition, as is the chemical affinity of fibrin for calcium (similar to that existing between calcium and the hyalin of hyaline cartilage and the collagen in which new connective tissue is so rich), which can serve to hold locally available the calcium liberated from dead bone at the site of the fracture. During the days just following the fracture the fluid portion of the hematoma is a factor of importance through its  $p_H$  in establishing the local source of calcium; if it is extensive and remains as fluid in situ (dependent on local circulatory efficiency), it may be a hindrance to the proper progress of the growth of granulation tissue (the effect of a fluid medium on the growth of tissue). The reputed backwardness in the healing of fractures bathed in synovial fluid is thus logically explained.

(c) The circulatory status of the part, including the tissue fluids, in early and late stages of fracture healing. The evidence supports the view that for the first week or so following a fracture there is normally a  $p_H$  definitely and often markedly to the acid side, dependent on elements cited under "local pathology" and under "biochemical status of the tissue fluids." The necessity for this acid  $p_H$  is discussed under 4. Relative circulatory stasis in the part is essential at this time to render available for use calcium derived from dead bone at the site of the fracture, decalcification of such bone occurring only in an acid medium. The circulatory stasis prevents the too rapid carrying off of the acid products of necrosis and autolysis which are largely responsible for the  $p_H$  status, and actually intensifies this status by its effect on the metabolism of the living cells present. The analogy may be aptly drawn between the status of the part as regards the  $p_H$  of tissue fluids and the carbon dioxide concentration in a given room. The parallel involves four main factors: (1) the number of people in the room, corresponding to the cell population in a given region of tissue; (2) the state of metabolic activity of those people—active, quiescent or in a state of death and dissolution—the parallel in the tissues is obvious; (3) the chemical characteristics of the air supplied to the room, corresponding to the qualitative circulatory status of a given part; (4) the rate of renewal of the air supplied to the room, corresponding to the quantitative circulatory status of a given part.

Similarly, following this initial period of stasis, a return to the normal circulatory status will be accompanied by a diminution in the acidity of tissue fluids, to a point compatible with the deposition of the freed calcium. This apparently occurs only in the presence of the more alkaline  $p_H$  (this holds true under all points of view advanced in the academic study of the exact mechanism of this deposition); when the fluid content of the hematoma is large and it has remained localized

and undiffused its diminution through the increased circulatory efficiency removes a definite bar to the growth of tissue.

Impairment of the circulatory status sufficient to cause massive necrosis is discussed under 1(a). The result of prolonged circulatory stasis with its effect on tissue metabolism and its maintenance of acidity in the  $p_H$  of tissue fluids is obvious. It is also obvious that when the amount of necrosis is extensive but not sufficiently massive to obviate the possibility of adequate growth of granulation tissue in replacement, the time needed to restore the  $p_H$  of tissue fluids to levels compatible with calcium deposition is in direct proportion to the interrelationship of two factors: the amount of necrosis and the speed of restoration of circulatory efficiency. In patients with a small amount of necrosis and with a normally rich circulatory apparatus the element of rapid restoration of a high degree of circulatory efficiency becomes a matter of relatively little importance in the treatment as regards the healing of bone. Proportionately to the increase in the amount of necrosis and the anatomic capabilities of the part as regards circulatory efficiency, this element becomes more and more important in the treatment from the standpoint of calcium deposition, viz., healing of bone.

(d) Chemical and physical bars to the healing of tissue. The influence of infection in producing continuous necrosis by chemical means, thus preventing primary healing, is obvious, and it has been demonstrated that with many suppurative processes there is established, even in the absence of extensive necrosis, an acid  $p_H$  resulting in the decalcification of bone and in but little or no calcium deposition in the granulation tissue which may, however, be overabundant. Unfortunately I am not aware of any investigation of the interesting question of the  $p_H$  of tissue fluid in low grade and relatively chronic infections characterized by increased formation of bone or exuberant callus after fracture. Included in the group of physical influences I should like to mention the effect of diathermy (considered as internally applied heat) and of roentgen rays. Diathermy under high milliamperage, as frequently used early in the treatment of fractures, may be, and unquestionably frequently is, a definite bar to healing by an actual devitalization of the tissue, aiding decalcification but interfering with the subsequent calcium deposition (factor 4). Its beneficial effect under any circumstances in this respect is highly problematic; if there is any, it can be exercised only at low milliamperages producing no damage to the tissues and can be of benefit only in relaxing vascular spasm to relieve congestion. It is highly improbable that after the first five to seven days constant local circulatory congestion can have any except a deterrent effect on calcium deposition. Exposure to roentgen rays is subject to the same general reservations.

(c) Mechanical bars to the growth of tissue. The rôle played by soft parts, including periosteal flaps, whether living or dead, and by large fragments of dense bone, if dead, as mechanical bars when interposed between the ends of the bone requires no discussion.

2. *Growth of Granulation Tissue.*—(a) This point is supported beyond dispute by clinical (including roentgenographic) and experimental evidence and holds true up to the point of massive necrosis as discussed under *b*.

(b) When necrosis becomes sufficiently massive it serves obviously as a bar to the growth of granulation tissue through the removal of all locally available sources for such growth.

(c) The anatomic characteristics of the part are frequently a reason for the lack of growth of granulation tissue. When a fracture occurs in a region such as the neck (intracapsular) of the femur or the proximal half of the carpal scaphoid there is naturally a varying amount of necrosis and circulatory damage. Because of the exceedingly minimal or even totally lacking circulatory status of the proximal bony fragment in each instance the source for the growth of granulation tissue and adequate accessory circulatory supply is in the surrounding soft parts. In the former case there is only the dense fibrous capsule; in the latter there is frequently nothing at all, or, at most, a mere bit of fibrous ligament. Thus scant growth of tissue occurs, often with so-called "aseptic" necrosis of the separated portion of bone. Even if some growth of granulation tissue is possible, it is hindered by the presence of synovial fluid (the effect of a fluid medium on the growth of tissue). In contrast to the femoral neck with its characteristic changes even when adequately reduced, one notes the intertrochanteric region but a few centimeters away, where, in a class of patients identical with those in the group with a fractured neck, the healing by bony union is not only profuse and rapid but occurs so universally that these fractures heal despite obvious gross mistreatment and under practically all conditions. The essential difference lies in the fact that the intertrochanteric region is buried in large fleshy and vascular muscular attachments—a rich accessory circulatory reservoir. The fluid may be a factor in all fractures involving joints sufficiently to allow the bathing of the fractured surfaces in synovial fluid. The factor of a deficient source for new tissue holds true in explanation (so far as the growth of tissue is concerned) of fractures at the junction of the lower and middle thirds of the tibia and similarly characteristic regions, where the soft parts surrounding the bone are largely skin, tendon and fascia providing a poor source of growth. The site in the tibia is particularly interesting from this standpoint since the inner face with a tightly overlying skin affords the scantiest growth of tissue and resultant healing

of bone; the external face, with its tendinous and areolar planes, affords but little more, and the posterior face, with its muscular attachments, shows the greatest amount of callus. The analogy to the neck of the femur and intertrochanteric region is obvious.

(*d*) The amount of fluid persisting over a long period at the site of the fracture offers a definite bar to the adequate growth of granulation tissue. A large hematoma which remains circumscribed and synovial fluid are good examples. It is to be remembered in the former case, however, that hematoma fluid has been shown after a number of days to contain a large percentage of calcium from the decalcified dead bone, and any efforts to get rid of it are therefore best made before such decalcification takes place, viz., at the onset of treatment. Late removal of such fluid, while it is an aid to the growth of tissue, withdraws some of the local calcium available for deposition in the new tissue.

(*e*) The elements *d* and *e* discussed under "Local Pathology" (clinical, physical and mechanical bars to tissue growth). The influence in this connection of the factors there discussed is obvious.

3. *Source of Local Calcium.*—Not only does the clinical evidence support the view that the effective source of the calcium used for callus in the primary healing process following fracture is the traumatized bone at the site of the fracture, but experimental evidence bears out the clinical findings and in the main adequately supports the view that the levels for blood calcium and phosphorus and the general calcium metabolism have no appreciable bearing on the question of primary healing of fractures and that as a source of calcium the dead bone at the site of the fracture can actually be substituted for by calcium salts of various types introduced in replacement of such dead bone or used as a source of calcium in soft parts unconnected with bone to produce actual ossification when the other factors involved in the process of the formation of new bone are concurrently reproduced. It must be remembered that the local source of calcium is only one in a complicated interrelationship of factors, and that, while there is evidence to show that it can be substituted for, the clinical application can be considered to be purely in an experimental stage and unpractical for use at the present time.

The local decalcification of dead bone, the rapid local concentration of calcium in the soft parts surrounding the site of the fracture, the independence of these two factors from variations, clinical and experimental, in calcium intake, output and balance are all supported by the major weight of published evidence and by personal observations.

(*a*) If the source of the calcium utilized in the ossification of the healing tissue following fracture is derived locally by decalcification of dead bone, the influence of the amount of necrosis in the bone is obvious.



(b) If, however, this dead bone is one large mass of dense cortical bone the actual amount of calcium made available is relatively small as compared with a similar aggregate of bone in the form of small comminuted fragments or of cancellous bone. It is merely a question of surface area exposed to the decalcifying action and of feasibility of ingrowth of the tissue. It is for this reason that in general chip grafts and thin osteoperiosteal grafts or shavings result in more profuse formation of bone than do massive cortical grafts, and that a massive graft which includes both the cortex and the underlying cancellous bone is more efficient than one which comprises merely the dense cortex.

(c) The influence of fibrin from the effused blood and of the collagen in which young connective tissue is so rich is a matter of importance in holding in situ the calcium made available under the conditions of factor 4. The adsorption affinity between calcium and these two substances is definite and is the explanation of why the calcium remains available locally instead of being rapidly carried away as soon as circulatory efficiency approaches the normal.

(d) The biochemical status of the tissue fluids is a vital influence.

4. *Biochemical Status of the Local Tissue Fluids.*—Regardless of the exact mechanism whereby decalcification of dead bone occurs to furnish available calcium and of the exact mechanism whereby such available calcium is deposited in the newly formed connective tissue to form bone, all the evidence supports the view that for the former there must exist an acid  $p_H$  in the local tissue fluid, and that such a  $p_H$  is incompatible with the deposition of calcium in the newly formed tissue, the latter process being possible only when the  $p_H$  has reverted to an approximation of the normal average  $p_H$  in tissue fluid, viz., relative (as compared with the stage of tissue death and autolysis) alkalinity. The parts played in the production of these two phases of  $p_H$  in tissue fluid by the factors of tissue death from whatever cause, rate of local cell metabolic activity, local cellular richness, anatomic characteristics of the part, qualitative and quantitative status of the local circulatory process (including lymphatic and tissue fluids) and infection, have already been indicated. It is also obvious that if the biochemical status of the part is unfavorable, calcium, even if present in dead bone, cannot be made available, or if made available cannot be utilized without a change in the condition of  $p_H$  responsible for making it available.

#### C. INFLUENCE OF THE STATED OBSERVATIONS ON THE TREATMENT OF FRACTURES

On the basis of these observations the process of healing in a fracture is one in which, following the injury and the resultant inflammatory process, an acid  $p_H$  of the local tissue fluids, dependent on the interrela-

tionship of tissue necrosis and circulatory efficiency, is associated with decalcification of the dead bone at the site of the fracture. Such liberated calcium is held locally by a chemical adsorption affinity between it and the fibrin of the hematoma and the collagen of the newly formed connective tissue—i. e., granulation tissue—growing from all directions along the fibrin network at the site of the injury, producing a local concentration of calcium about the fracture. With increasing cell metabolism, and with interrelated increasing efficiency of circulation and carrying away of the products of necrosis, there is a reversion of this acid  $p_H$  to the alkaline side, and coincident with this change there occurs a deposition of the local adsorbed calcium in the newly formed connective tissue to form new bone. Evidence has been listed to support this point of view. If it is correct, methods of treatment can help the healing by aiding, if necessary:

(a) The establishment of the early acid  $p_H$  in local tissue fluids at the site of the fracture.

(b) The adequate growth of granulation tissue.

(c) The reversion at an early date to a relatively alkaline  $p_H$  in the local tissue fluids which will allow calcium deposition in the newly formed tissue.

(d) The maintenance of a proper interrelationship between the local metabolic activity and the circulatory efficiency.

There is no difficulty in establishing an early acid  $p_H$ . The chief danger lies in such extensive tissue death and relative circulatory inefficiency that this primary state may persist long beyond its useful stage and become a hindrance by subsequently interfering with calcium deposition. It may be considered practically impossible to restore circulatory efficiency and the coincident increased cellular metabolism with removal of products of necrosis so rapidly as to interfere with the adequate operation of tissue fluid  $p_H$  on the acid side.

In fresh fractures the local source of calcium is therefore readily established. It is extremely doubtful whether the introduction artificially of a local source of calcium in fresh uncomplicated fractures is ever necessary. If such an introduction is ever made clinically useful it will be in cases in which there is a definite loss of substance with a deficit of bone—i. e., of local calcium—or in old cases of delayed union and nonunion, in which the primary stage has been passed and a markedly avascular and noncalcified tissue occupies the region of the fracture, and then only when, coincident with the introduction of the source of calcium, the other factors involved can be established, as is the case when the operation of bone grafting is done successfully. Attention has previously been invited to the operation of this factor in the amount of bone production following various types of bone grafts.

The adequate growth of granulation tissue is dependent on an adequate source for such growth, viz., available vascularly active tissue, and the absence of deterrent agents such as excess fluid, infection and mechanical factors.

Failure of growth of granulation tissue is a frequent cause of inadequate callus. In general, one can say that the restoration of the circulatory status of the part to that approximating normal for the patient as early and as fully as possible should be the aim of treatment designed to influence this factor. The most effective means of doing so is the active use, within pain limits, of the muscular apparatus of the part from the beginning of the treatment. Proportionately as the chosen method departs from this ideal one adversely influences the growth of granulation tissue as well as the biochemical element. Active and painless muscular contraction produced by artificial (electrical stimulation) means is a relatively inefficient substitute. If this is impossible, painless gentle massage (early) may at least relax muscular and vascular spasm sufficiently to improve the local circulation. Absolute immobility of the part as a whole is least apt to aid adequate granulation tissue healing. Moreover, in cases in which the source of granulation tissue is deficient because of the anatomic characteristics of the part, as heretofore described, operative intervention—under proper circumstances as regards organization, personnel, equipment and patient—may well be indicated as the primary procedure, if, as a result of operation, not only good position but also new sources of growth of granulation tissue are obtained and early active muscular activity is made possible by rigidity of fixation at operation. In general, it can be said that healing is slower following operative care in fresh fractures than after closed treatment, except when active motion of the part is possible shortly after operation, assuming, of course, that the operative procedure is or can be so performed that extensive tissue necrosis and vascular damage are not concomitants. This is a matter for consideration in fractures in the regions referred to previously where the anatomic characteristics of the part are a bar to healing. Incidentally, as a corollary, no operative reduction should be performed under any conditions, except as a matter of necessity, unless the method of operative fixation allows early active function (if necessary through the aid of balanced suspension to relieve strain). External fixation of the part as a whole following operation is, I am convinced, commonly followed by delay in adequate callus formation for the reasons stated. Obviously, also, this has no bearing when operative reduction is a matter of necessity (in interposition of tissue, in inability to reduce otherwise, etc.), the purpose of the operation then being reduction, and it may be impossible to accomplish more than to secure a satisfactory position.

The influence of local collections of fluid on adequate growth of granulation tissue is effective in fractures of the joints through the presence of synovial fluid, and it is not evident how this factor can be obviated. On the other hand, when the accumulated and persistent collection of fluid is from hematoma, early circulatory efficiency aids in diminishing it and can be greatly helped, when the effusion of blood is obviously great, by aspiration. This aspiration should be done early, for when it is delayed the fluid contains a large amount of calcium, which is necessarily removed with it. It is also obvious that violent and repeated attempts at reduction by increasing the amount of necrosis destroy sources of granulation tissue and that operative technic must be of the gentlest and most "tissue economical" type to avoid such a result.

It is also true that, since the interrelationship of necrosis, circulatory efficiency and local cell metabolic activity determines the biochemical status of the local tissue fluids throughout the healing process, the statements made as to the possible bearing of treatment on adequate growth of granulation tissue apply equally to the question of the proper biochemical status of  $p_H$  in tissue fluids. The use of diathermy in high milliamperage and the practice of frequent or prolonged exposures to roentgen rays may interfere seriously with the healing of fractures. The use of antiseptic solutions of acid reaction in compound fractures interferes with healing. This is often clinically true of the use of surgical solution of chlorinated soda which is not carefully titrated and freshly made, which is frequently accompanied by actual decalcification of bone and slow healing. Lastly, the administration or use of agents designed to affect the general body metabolism or to affect specifically the calcium and phosphorus metabolism is without appreciable value in the treatment of fractures.

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#### ABSTRACT OF DISCUSSION

DR. F. J. GAENSLER, Milwaukee: My experience with the introduction of a calcium depot in the form of calcium phosphate and calcium carbonate at the site of nonunion or delayed union is limited. In one of the cases of nonunion I drilled holes through the ends of the bone, following Boehler's technic, and then injected calcium phosphate and calcium carbonate in the form of a paste into these holes, but this proved unsuccessful. I know of at least one case in which infection followed the use of such a powder, and I am perfectly willing to let the pioneers in this work pave the way a bit farther. While I can, therefore, add nothing to this phase of the subject from clinical experience, I should like to ask a few questions.

Schanz and others have found that a high osteotomy as a palliative procedure for ununited fracture of the neck of the femur frequently resulted in bony union. This procedure does away with the shearing or wearing away effect on the neck

of the femur and establishes weight bearing on the fractured ends in a line practically perpendicular to the line of the fracture. I saw one of these cases in Boehler's clinic in 1929 one year after a high Schanz osteotomy and two years after the original injury. Bony union had resulted, and the patient walked with only a moderate limp and no pain. This was the first case which I had the opportunity of observing in which late union occurred. Later, while visiting Schanz in Dresden, I described this case to him, and he informed me that in these cases late union is not at all unusual. In a series of twelve cases which Camitz recently reported late union occurred in five, while in another of recent date the results appeared favorable. Thus, in this series of twelve cases, practically half went on to late union. Nonunion is generally attributed to insufficient blood supply, but in these cases the osteotomy in no way interfered with the actual site of the fracture, so that one must find some other explanation for success in this group.

Many years ago Hugh Owen Thomas advised percussion and damming at the site of the delayed union. Rubber constriction bands were placed above and below; the site of the fracture, protected with a felt pad, was then hit repeatedly with a wooden mallet. This was successful in many instances. I should like to hear Dr. Murray discuss these clinical observations in the light of his recent work.

DR. CLAY RAY MURRAY: The difficulty of clearly presenting so complex a subject in a short time is great. One must not consider the local source of calcium alone as the essential factor in healing. It is only one in a complicated interrelationship of factors. The four factors involved are: tissue necrosis, growth of granulation tissue, the local source of calcium and the biochemical status of the local tissue fluids, dependent in part on the interrelationship between tissue necrosis and vascular efficiency.

From the standpoint of these four factors an analogy exists between the intertrochanteric region and the radial site used in my experimental work and the neck of the femur and the ulnar site used by Dr. Key. The radius is covered by vascular muscular attachments, as in the intertrochanteric region, and the ulna is subcutaneous—analogueous to the vascularly poor soft parts about the femoral neck; this is an important factor.

Dr. Compere quotes work on the carpal bones. They rate with the tibia and ulna. Regardless of the calcium element the vascular factor results in nonunion.

An analysis of experimental results must include a consideration of all four factors and not only of the local source of calcium.

In the nineteenth edition of Lexer's "Allgemeine Chirurgie" the vascular situation during fracture healing is illustrated by injection into experimental animals. This demonstration definitely shows that the increased vascularity occurring after fracture is almost entirely in the periosteum and the surrounding soft parts.

Stirling in Edinburgh and Rollo in Italy have both secured healing in bone gaps (radius) employing solutions of calcium instead of the powder as I did.

As to the influence of the periosteum on osteogenesis except as a transmitter of circulation from the soft parts, Bancroft in 1912 removed all of the periosteum and endosteum possible and obtained a solid union with chip grafts.

There is a difference between the results obtained with a bone that has been boiled for one minute and those obtained with one that has been boiled for ten minutes. The latter results in less satisfactory, often defective, union.

We have secured solid union with boiled bone after a 4 inch (10.16 cm.) fibular resection and with the powdered calcium in other bones after preliminary alkalinization with hundredth-normal solution of sodium carbonate.

In delayed union percussion and damming depend on biochemical changes secondary to vascular changes. In the fracture of the femoral neck in which union occurs only if strain is borne in such wide abduction that there is a jamming together of the fragments of the neck instead of a shearing strain on the fibrous union, as in ordinary weight bearing, the explanation lies in the torsional strain present in the latter instance, which decreases the circulatory efficiency of the soft tissues.

In all these situations the circulatory factor is the difficult one to analyze. For example, Morton has published two analyses of the effect of venous interference on the healing of fractures with diametrically different solutions.

I believe that the effect of diathermy is purely theoretical and lacks adequate clinical or experimental support.

DR. EDWARD L. COMPERE, Chicago: Dr. Murray's interesting explanation of the biochemical factors in the healing of fractures can be accepted if one also recognizes the influence of the osteoblasts themselves acting in the medium which he has described.

Dr. William Stewart, working as a Fellow in orthopedic surgery at the University of Chicago, carried out a series of experiments similar to those made by Dr. J. Albert Key of St. Louis, with the exception that he not only removed a segment of bone from the ulna and the tibia but removed the periosteum as well. The experiments were well controlled. On the one side he placed the calcium salts which had been recommended by Dr. Murray, and on the other side he replaced the fragments of bone or an entire section of bone as in the cases described by Dr. Key. In one series of experiments the calcium salts were put into bags made from fascia lata before being placed in the bone defect. In each instance all the calcium salts were absorbed, and union did not occur in a single instance. When bone that had been boiled long enough (from fifteen to twenty minutes) to destroy the bone cells was used instead of the calcium salts, it also failed to bring about union. It is known that if the periosteum is stripped and a section of bone excised, as shown by Dr. Key in his controls, the defect may be repaired, but in the experiments under consideration the periosteum as well as the bone was removed. All the chemical factors enumerated by Dr. Murray should have been present and the calcium salts were available, but no bone was formed and the calcium was absorbed.

The belief held in the clinics of the University of Chicago is that one important factor in the healing of fractures in nonunion, and particularly in such cases as congenital nonunion, is the presence of living bone cells. The use of the massive bone graft is preferred in such cases, partly because of the splinting effect of the graft.

I agree with Dr. Key that in cases in which the serum calcium and inorganic phosphates and the  $pH$  of the blood are normal living bone cells acting in the ideal medium described by Dr. Murray should be capable of taking the calcium salts from the blood stream and bringing about union, without the addition of any inorganic salts.

I believe that there is an important element to be found in living bone which is not present either in boiled bone or in the inorganic calcium salts.

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# QUANTITATIVE STUDY OF THE RATE OF HEALING IN BONE

## II. NORMAL RATE OF HEALING

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It is essential that the normal rate of healing be definitely established before any attempt is made to determine the effect of various conditions and substances on the rate of healing. Once this normal rate is established it should be comparatively easy to estimate the amount of variation produced by such factors as diet, incomplete mobilization of fractured bones, the injection or deposit of substances at the site of fracture and all the other procedures which have been advocated to increase the rate of healing in bone and prevent nonunion.

Although the results reported in this article appear to establish the normal time required for healing, it is proposed to recheck them with the results obtained in experiments on another series of animals, in which more factors are held constant, before this rate of healing is accepted as a standard with which to compare variations from the normal.

The method used in this study has been described in a previous publication.<sup>1</sup> Three factors of strength were measured in each bone, i. e., tensile strength, resistance to torsion and resistance to bending. The data for each of these measures, as well as the data for weight of the bone, were analyzed. This analysis of data was made under the direction of Dr. Edith Boyd of the Institute of Child Welfare and the department of anatomy.

### TENSILE STRENGTH

The data were separated into two categories: (1) those concerning nonfractured ulnas and (2) those concerning fractured ulnas. The latter group of bones was subdivided into: (a) those which healed within from nine to twenty days. (b) those which healed within from twenty to forty days and (c) those which healed within from forty to

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TABLE 1.—*Tensile Strength and Weight of Bone in Nonfractured and Fractured Ulna*

Rabbit	Right Nonfractured Ulna		Days Required for Healing	Left Fractured Ulna	
	Weight of Bone, Gm.	Tensile Strength, Kg.		Weight of Bone, Gm.	Tensile Strength, Kg.
101.....	1.680	45.4	8	1.880	....
98.....	1.450	45.4	9	1.650	5.0*
99.....	1.600	31.8	11	1.850	2.7
13.....	1.810	23.6	12	2.090	2.7
8.....	1.750	28.7	12	2.300	3.4
100.....	1.800	43.5	12	2.200	5.0
83.....	1.750	52.4	13	1.850	3.2*
11.....	1.720	25.9	14	1.950	4.1
17.....	1.550	39.7	14	2.200	3.4
85.....	1.050	29.0	15	1.350	4.1*
84.....	1.200	42.6	16	1.500	7.3*
78.....	1.600	44.9	17	1.900	5.4*
74.....	.....	47.2	17	.....	7.3*
88.....	2.500	51.3	17	2.280	3.2*
28.....	2.300	25.4	17	2.900	15.4
5.....	2.100	26.8	17	1.910	4.5
21.....	2.150	41.3	18	2.550	13.6
22.....	1.550	29.5	18	1.450	11.3
6.....	1.210	21.9	18	1.360	....
18.....	1.150	.....	19	1.600	6.8
19.....	1.500	22.7	20	2.000	22.7
60.....	1.100	28.1	20	1.600	10.9*
7.....	1.670	23.1	20	1.960	9.9*
15.....	1.900	25.4	21	2.350	8.2
55.....	.....	45.4	21	.....	....
10.....	1.570	16.9	22	1.750	0.0
48.....	1.300	40.8	23	.....	....
93.....	1.540	44.7	23	1.780	17.9*
91.....	1.630	44.2	23	1.800	26.3*
92.....	.....	42.2	24	.....	11.8*
94.....	.....	46.5	25	.....	13.6*
95.....	.....	23.8	26	.....	13.6*
96.....	.....	38.1	27	.....	32.7*
2.....	1.675	29.3	28	1.980	14.3
30.....	1.950	53.3	29	2.060	9.1*
82.....	.....	29.5	29	.....	15.4*
31.....	1.600	39.9	29	.....	....
81.....	.....	29.5	30	.....	11.8
87.....	.....	29.9	31	.....	16.3*
1.....	1.350	14.9	33	1.440	....
77.....	1.550	51.5	34	1.950	....
76.....	1.600	33.6	34	1.850	26.3*
73.....	.....	36.3	36	.....	28.6*
72.....	.....	32.5	37	.....	29.9
71.....	.....	31.3	38	.....	30.8*
23.....	1.500	.....	39	1.425	26.8*
20.....	1.050	24.0	40	1.300	7.3
90.....	.....	25.6	42	.....	27.9*
102.....	.....	47.2	43	.....	19.5
89.....	.....	31.8	45	.....	28.4*
24.....	.....	36.3	46	.....	13.4*
80.....	.....	20.0	47	.....	....
79.....	.....	20.9	49	.....	20.0*
70.....	.....	47.2	50	.....	20.9*
69.....	.....	42.6	52	.....	30.2*
68.....	.....	46.4	56	.....	24.9
65.....	.....	20.9	58	.....	24.9*
63.....	.....	38.8	61	.....	20.9
62.....	.....	32.0	63	.....	25.6
67.....	.....	40.4	66	.....	26.3
53.....	.....	34.2	66	.....	19.5*
106.....	1.538	27.7	77	1.760	5.7*
107.....	1.791	45.4	93	2.085	40.8*
105.....	1.770	40.8	93	.....	17.7
113.....	1.228	20.9	94	1.265	18.0*
111.....	1.383	49.3	94	1.962	20.3
112.....	1.824	24.6	96	2.147	35.6
120.....	1.333	28.2	100	1.555	30.5*
108.....	2.070	13.8	107	2.722	20.4*
123.....	1.889	46.5	108	1.892	32.3*
125.....	1.802	58.4	108	2.390	20.9
124.....	1.781	44.5	113	2.116	28.7*
119.....	2.053	36.6	113	2.040	49.5*

TABLE 1.—*Tensile Strength and Weight of Bone in Nonfractured and Fractured Ulna—Continued*

Rabbit	Right Nonfractured Ulna		Days Required for Healing	Left Fractured Ulna	
	Weight of Bone, Gm.	Tensile Strength, Kg.		Weight of Bone, Gm.	Tensile Strength, Kg.
122.....	1.590	45.9	114	1.726	24.2*
121.....	1.524	39.6	114	1.586	19.5*
110.....	.....	28.4	118	.....	24.5
109.....	2.145	29.7	125	2.500	23.1*
117.....	1.795	36.1	125	2.115	26.3
118.....	1.401	32.7	131	1.565	41.4
114.....	2.105	36.6	135	2.334	29.4
115.....	1.900	55.7	135	1.927	29.9*
116.....	1.625	55.0	138	1.800	29.9*
134.....	1.855	70.2	139	2.385	26.3*
135.....	1.971	84.6	140	2.141	44.8
137.....	1.576	62.9	140	1.857	40.3
133.....	2.117	62.0	145	2.195	43.8*
132.....	1.763	28.0	145	2.038	27.9*
131.....	1.613	64.4	152	1.723	50.0*
126.....	1.943	56.6	158	3.749	35.2
130.....	1.906	60.0	158	2.239	47.5
136.....	1.535	60.6	159	1.605	41.7
129.....	1.509	43.0	159	1.861	24.9
125.....	1.957	66.8	191	2.360	50.6*
127.....	2.202	73.7	191	2.530	25.6*

\* Separated at line of the fracture.

two hundred days. The last two groups were combined into those which healed within from twenty to two hundred days.

Measurements of tensile strength were made on the nonfractured right ulnas of ninety-two animals and on the fractured left ulnas of eighty-five animals. The subdivisions of the group of fractured ulnas were made according to the number of days intervening between the time of the fracture and the killing of the animal, when the measurements were made.

The data are listed in table 1; they are arranged according to the number of days the animal lived after the fracture was produced.

A regression line formula was computed for the group of nonfractured ulnas and for each of the subdivisions of the group of fractured ulnas. The regression line and the individual observations for the group of nonfractured ulnas are shown in figure 1 *A*. The regression line indicates an increase in the tensile strength of the nonfractured ulna during the period of study. Since the average span of life in the rabbit is from five to six years, two hundred days represents a considerable part of the life of this animal. Therefore, the increase noted in tensile strength is probably due to changes caused by age. These changes may have been due to increased weight or to physical or chemical changes in the bone. That they were not due to increase in weight but rather to physical or chemical changes was indicated by a partial correlation of the data for the nonfractured ulna. This partial correlation was determined for tensile strength, weight and time the animal lived after the operation. It is especially indicated by the standard error of tensile strength when this is computed with variable weight and

time, with the constant weight and variable time, with the constant time and the variable weight and with constant weight and time. The results are given in the section "Comment."

The regression line for the nonfractured group is compared with the data for the fractured group in figure 1 *B*, which includes a field graph of the data for the nonfractured ulnas and a point-to-point curve through the mean values for the tensile strength of the fractured ulnas, computed for ten and twenty day intervals. These groups of data for the fractured ulnas, the number of observations made and the means are as follows:

Days required for healing	10-20	20-30	30-40	40-60	60-80	80-100	100-120	120-140	140-160	160-180	180-200
Number of observations	18	13	7	10	5	5	10	9	5	0	6
Mean.....	6.0	15.9	24.7	21.7	19.6	26.5	27.1	29.7	41.4	0	37.6

The point-to-point curve shows a rapid increase in the tensile strength of the healing bone until after the thirtieth day of healing;

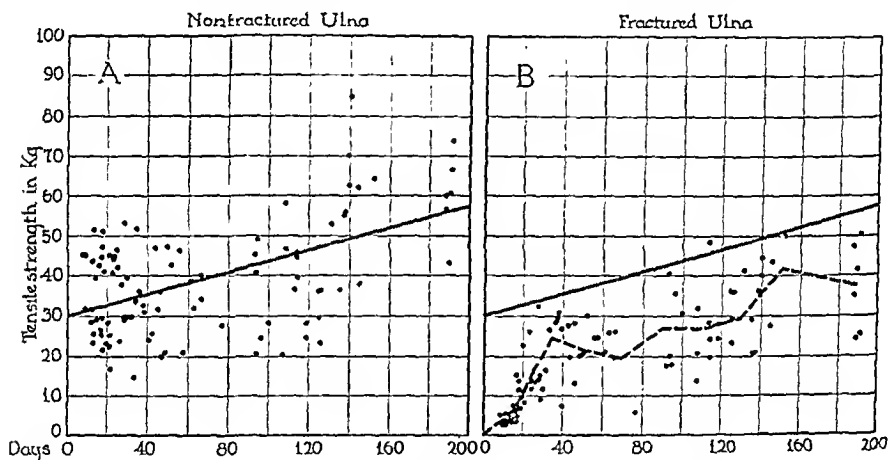


Fig. 1.—*A*, graph for the tensile strength of the nonfractured ulna, with regression line (formula:  $TS [\text{tensile strength}] = 30.2736 + 0.137 D [\text{days}]$ ). *B*, graph for tensile strength of the fractured ulna. The broken line is a point-to-point curve through mean values computed for ten and twenty day intervals; the unbroken line is the regression line of the nonfractured ulna.

thereafter the increase in tensile strength is approximately that found in the nonfractured ulna and is therefore probably due to the same changes in the bone.

In order to check this observation, regression line formulas were computed for certain subdivisions of the fractured group, i. e., bones which required from nine to twenty days for healing (eighteen cases), those which required from twenty to forty days (twenty cases), those requiring from forty to two hundred days (forty-seven cases) and those requiring from twenty to two hundred days (sixty-seven cases). These regression lines are shown in figure 2. The regression line of the control group is included for comparison. This demonstrates a rapid increase in

tensile strength between the ninth and twentieth day after fracture and a similar increase between the twentieth and fortieth day of healing, but after the fortieth day of healing there appeared to be no tendency for the bone to regain its original strength. It remained definitely weaker, gaining strength at approximately the same rate shown by the nonfractured bone in which there were changes due to age. Therefore, it may be stated that, so far as tensile strength is concerned, healing in the ulna of the rabbit does not reproduce the original strength of the bone, but it is terminated within less than forty days.

In taking these measurements on eighty-five previously fractured ulnas, not all were found to be separated through the healing fracture; instead, the bone in part of them was separated or pulled apart at some other point. In the earlier experiments, no record was kept of the point of separation. Later, however, a record was kept. Forty-nine

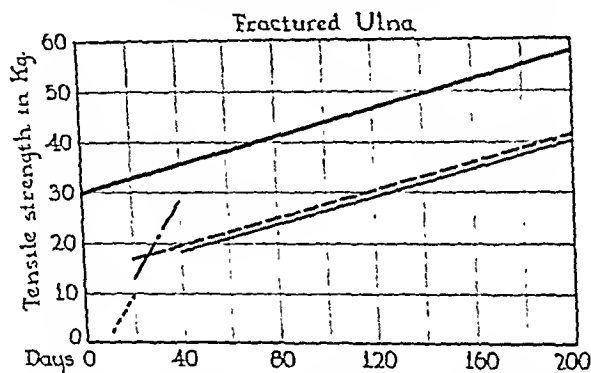


Fig. 2.—Regression lines for tensile strength of the fractured ulna. The line with short dashes indicates the period of from nine to twenty days (formula:  $TS = 5.26 + 0.7573 D$ ); the line with the long and short dashes, the period of from twenty to forty days (formula:  $TS = -3.13 + 0.7849 D$ ); the lower unbroken line, the period of from forty to two hundred days (formula:  $TS = 14.06 + 0.1335 D$ ), and the line with long dashes, the period of from twenty to two hundred days (formula:  $TS = 14.68 + 0.1299 D$ ); the upper unbroken line is the regression line of the nonfractured ulna.

bones were recorded as having separated at the line of fracture (indicated by the asterisk in table 1), and in thirty-six cases either no notation concerning the point of separation was made or the bones were recorded as having separated outside the line of fracture. These thirty-six cases make up the group called fractured ulnas not separated at the line of fracture.

For the purpose of analysis, the data for both groups—ulnas not separated at the line of fracture and those separated at this line—were subdivided according to the number of days the animal lived after the operation before it was killed. These data are as follows:

	Not Separated at Line of Fracture				Separated at Line of Fracture			
Days required for healing.....	0-20	20-40	40-200	20-200	0-20	20-40	40-200	20-200
Number of cases in group.....	11	5	20	25	7	15	27	42

TABLE 2.—Means of Tensile Strength for Nonfractured and Fractured Ulnas

Nonfractured Ulna		Fractured Ulna				R	P
Number of Cases	Mean $\pm$ Standard Error, Degrees	Number of Cases	Duration of Healing, Days	Mean $\pm$ Standard Error, Degrees	Difference $\pm$ Standard Error		
92	39.32 $\pm$ 1.4523	18	9-20	6.02 $\pm$ 0.8627	33.30 $\pm$ 1.6892	19.71	>0.00
		20	20-40	18.85 $\pm$ 1.7911	20.47 $\pm$ 2.3059	8.88	>0.00
		47	40-200	28.46 $\pm$ 1.5593	10.86 $\pm$ 2.1309	5.10	>0.00
		67	20-200	25.59 $\pm$ 1.3316	13.73 $\pm$ 1.9704	6.97	>0.00

TABLE 3.—Regression Coefficients of Tensile Strength and Time for Nonfractured and Fractured Ulnas

Nonfractured Ulna		Fractured Ulna				R	P
Number of Cases	b $\pm$ Standard Error	Number of Cases	Duration of Healing, Days	b $\pm$ Standard Error	Difference $\pm$ Standard Error		
92	0.1370 $\pm$ 0.0230	18	9-20	0.7573 $\pm$ 0.2692	-0.6203 $\pm$ 0.2702	2.30	0.02
		20	20-40	0.7849 $\pm$ 0.2500	-0.6479 $\pm$ 0.2511	2.58	0.01
		47	40-200	0.1335 $\pm$ 0.0288	0.0035 $\pm$ 0.0369	0.09	0.93
		67	20-200	0.1299 $\pm$ 0.0199	0.0071 $\pm$ 0.0304	0.23	0.82

TABLE 4.—Means of Tensile Strength for Fractured Ulnas Separated Outside Line of Fracture and Those Separated at Line of Fracture

Fractured Ulna Not Separated at Line of Fracture			Fractured Ulna Separated at Line of Fracture				R	P
Number of Cases	Duration of Healing, Days	Mean $\pm$ Standard Error, Degrees	Number of Cases	Duration of Healing, Days	Mean $\pm$ Standard Error, Degrees	Difference $\pm$ Standard Error		
11	9-20	6.63 $\pm$ 1.3236	7	9-20	5.07 $\pm$ 0.6085	1.56 $\pm$ 1.4568	1.07	0.28
5	20-40	17.38 $\pm$ 3.5195	15	20-40	19.33 $\pm$ 2.0707	-1.95 $\pm$ 4.0835	0.48	0.63
20	40-200	29.24 $\pm$ 2.3099	27	40-200	27.89 $\pm$ 2.0958	1.35 $\pm$ 3.1190	0.43	0.67
25	20-200	26.87 $\pm$ 2.1920	42	20-200	24.83 $\pm$ 1.6634	2.04 $\pm$ 2.7517	0.74	0.46

TABLE 5.—Regression Coefficients of Tensile Strength and Time of Healing for Fractured Ulnas Separated Outside Line of Fracture and Those Separated at Line of Fracture

Fractured Ulna Not Separated at Line of Fracture			Fractured Ulna Separated at Line of Fracture				R	P
Number of Cases	Duration of Healing, Days	b $\pm$ Standard Error	Number of Cases	Duration of Healing, Days	b $\pm$ Standard Error	Difference $\pm$ Standard Error		
11	9-20	1.1077 $\pm$ 0.3673	7	9-20	0.1503 $\pm$ 0.2550	0.9574 $\pm$ 0.4471	2.14	0.03
5	20-40	0.6329 $\pm$ 0.6298	15	20-40	0.8401 $\pm$ 0.2599	-0.2072 $\pm$ 0.6933	0.30	0.76
20	40-200	0.1494 $\pm$ 0.0357	27	40-200	0.1176 $\pm$ 0.0454	0.0318 $\pm$ 0.0574	0.55	0.59
25	20-200	0.1461 $\pm$ 0.0277	42	20-200	0.1191 $\pm$ 0.0255	0.0270 $\pm$ 0.0400	0.68	0.51

Regression line formulas were computed for each of these groups. The regression lines which they represent and a field graph of the distribution of the cases for both the ulnas which separated outside the line of fracture and those which separated through the site of fracture are shown in figure 3.

Comparison of the means and regression coefficients for all the regression lines computed for the data on tensile strength is made in tables 2, 3, 4 and 5.

#### TORSION

The data obtained in measuring resistance to torsion are given in table 6. The analysis of these data was more difficult than the analysis of the data for tensile strength, because the weight added was not the same in each experiment. This difficulty was surmounted in the following way: It was obvious that a straight line could be fitted to the

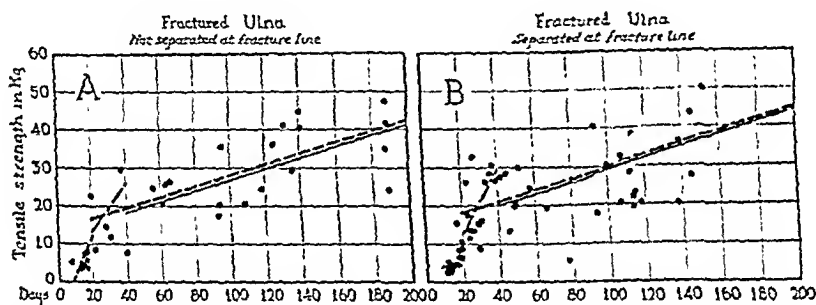


Fig. 3.—*A*, graph for tensile strength of the fractured ulna not separated at the line of fracture. The line with short dashes indicates the period of from nine to twenty days (formula:  $TS = 9.89 + 1.1077 D$ ); the line with long and short dashes, the period of from twenty to forty days (formula:  $TS = 0.17 + 0.6329 D$ ); the unbroken line, the period of from forty to two hundred days (formula:  $TS = 12.34 + 0.1494 D$ ), and the line with long dashes, the period of from twenty to two hundred days (formula:  $TS = 12.85 + 0.1461 D$ ). *B*, graph for tensile strength of the fractured ulna separated at the line of fracture. The line with short dashes indicates the period of from nine to twenty days (formula:  $TS = 2.84 + 0.1503 D$ ); the line with long and short dashes, the period of from twenty to forty days (formula:  $TS = 4.42 + 0.8401 D$ ); the unbroken line, the period of from forty to two hundred days (formula:  $TS = 15.67 + 0.1176 D$ ), and the line with long dashes, the period of from twenty to two hundred days (formula:  $TS = 15.67 + 0.1191 D$ ).

data if the measurements taken after addition of the first 10 Gm. of weight were not included. It seemed justifiable to assume that the readings taken after the addition of 10 Gm. of weight were too low because of resistance other than elasticity of the bone in the experimental set-up. They were therefore disregarded in calculating the regression line for these data. A scatter diagram of the measurements



TABLE 6.—Resistance to Torsion of Nonfractured and Fractured Ulnas

Rabbit	Nonfractured Ulna							Days Required for Healing	Fractured Ulna							
	Weight Added, Gm.								Weight Added, Gm.							
	0 to 10	0 to 20	20 to 40	40 to 60	60 to 80	80 to 100	40 to 90		0 to 10	0 to 20	20 to 30	30 to 40	40 to 60	60 to 80	80 to 100	40 to 90
Torsion, Degrees									Torsion, Degrees							
101	—	0.4	0.3	0.5	—	—	—	8	—	—	—	Too weak	—	—	—	
98	—	0.4	0.5	0.5	0.5	0.6	—	9	6.2	7.0	6.0	—	—	—	—	
99	—	0.3	0.4	0.4	0.5	0.5	—	11	39.2	—	—	Too weak	—	—	—	
8	—	—	0.9	1.0	0.8	0.7	—	12	—	—	—	Too weak	—	—	—	
13	—	—	0.9	1.0	1.0	1.1	—	12	—	—	—	Too weak	—	—	—	
100	—	0.2	0.3	0.4	0.3	0.4	—	12	3.1	6.1	—	—	—	—	—	
83	—	0.3	0.3	0.3	0.4	0.4	—	13	10.5	12.0	4.0	—	—	—	—	
11	—	—	0.5	0.9	1.0	0.8	—	14	—	—	—	1.3	1.7	2.0	—	
17	—	—	1.5	2.5	1.0	2.0	—	14	2.9	5.5	—	Too weak	—	—	—	
85	—	0.6	0.8	0.9	0.8	1.1	—	15	2.2	5.7	—	—	—	—	—	
84	—	0.5	0.7	0.8	0.7	0.7	—	16	1.5	3.2	2.0	—	—	—	—	
28	—	0.5	0.5	0.4	0.4	0.5	—	17	—	0.4	—	0.7	0.6	0.7	0.9	
74	—	0.6	0.6	0.6	0.6	0.7	—	17	2.5	6.5	3.0	—	—	—	—	
88	—	0.3	0.4	0.5	—	—	—	17	0.9	2.2	—	—	—	—	—	
5	—	—	0.5	0.4	0.4	0.7	—	17	—	0.8	—	0.4	0.6	0.9	—	
78	—	0.3	0.5	0.4	0.5	0.5	—	17	3.0	6.0	5.0	—	—	—	—	
22	—	0.8	1.4	2.2	2.7	2.6	—	18	—	0.5	—	0.9	1.1	1.1	—	
21	—	0.5	0.5	0.6	0.5	0.7	—	18	—	0.7	—	0.8	0.8	1.0	—	
6	—	—	0.7	0.6	0.9	0.9	—	18	—	—	—	—	—	—	—	
18	—	—	—	—	—	—	—	19	3.4	6.0	2.4	—	—	—	—	
7	—	—	0.9	1.0	0.9	1.0	—	20	—	—	—	1.6	1.9	1.6	—	
19	—	0.9	1.0	1.2	1.0	1.9	—	20	—	0.6	—	1.0	1.0	0.7	0.9	
60	—	0.6	0.9	0.8	1.2	1.3	—	20	—	1.2	—	2.1	1.9	2.3	—	
15	—	0.3	0.4	0.5	0.5	0.4	—	21	—	0.9	—	1.2	1.1	1.2	1.1	
55	—	0.4	0.5	0.6	0.5	0.6	—	21	Displacement of fragments							—
10	—	—	0.5	0.7	0.6	0.9	—	22	—	—	—	0.9	0.7	0.6	0.9	
48	—	0.4	0.4	0.4	0.5	0.5	—	23	Osteomyelitis							—
93	—	0.4	0.3	0.6	—	—	—	23	0.4	0.8	0.5	—	—	—	—	
91	—	0.3	0.4	0.4	—	—	—	23	0.3	0.5	0.2	—	—	—	—	
92	—	0.4	0.3	0.4	—	—	—	24	0.3	0.6	0.5	—	—	—	—	
94	—	0.3	0.5	0.5	—	—	—	25	0.2	0.5	0.4	—	—	—	—	
95	0.2	0.6	—	—	—	—	—	26	0.4	0.9	—	—	—	—	—	
96	0.3	0.5	—	—	—	—	—	27	0.3	—	—	—	—	—	—	
2	—	1.1	1.3	1.2	1.3	1.4	—	28	—	0.5	—	0.7	0.8	0.53	—	
82	0.2	0.4	—	—	—	—	—	29	0.3	0.5	—	—	—	—	—	
31	—	0.4	0.3	0.5	0.6	0.5	—	29	Slough of soft parts over fracture							—
30	—	0.3	0.5	0.4	0.5	0.5	—	29	0.8	1.7	0.5	1.1	—	—	—	
81	0.3	0.7	—	—	—	—	—	30	2.1	—	—	—	—	—	—	
87	0.3	0.5	—	—	—	—	—	31	0.9	—	—	—	—	—	—	
1	—	—	0.9	1.0	1.1	1.0	—	33	4.1	7.2	3.0	—	—	—	—	
77	—	0.4	0.3	0.5	—	—	—	34	0.2	0.5	0.3	—	—	—	—	
76	—	0.3	0.4	0.5	—	—	—	34	0.2	0.4	0.3	—	—	—	—	
73	—	0.5	0.5	0.5	—	—	—	36	0.3	0.6	0.3	—	—	—	—	
72	0.2	0.4	—	—	—	—	—	37	0.3	0.6	—	—	—	—	—	
71	0.2	0.4	—	—	—	—	—	38	0.2	0.5	—	—	—	—	—	
23	—	1.0	1.1	1.1	1.5	1.4	—	39	—	1.0	—	1.2	1.3	1.3	1.3	
20	—	2.0	1.0	2.6	1.9	—	—	40	—	1.0	—	1.3	1.2	1.4	—	
90	0.2	0.4	—	—	—	—	—	42	0.1	0.3	—	—	—	—	—	
102	0.2	0.4	—	—	—	—	—	43	0.2	0.4	—	—	—	—	—	
89	0.2	0.6	—	—	—	—	—	45	0.3	0.5	—	—	—	—	—	
24	0.2	0.4	—	—	—	—	—	46	0.2	—	—	—	—	—	—	
80	0.4	0.8	—	—	—	—	—	47	0.5	1.1	—	—	—	—	—	
79	0.3	0.6	—	—	—	—	—	49	0.3	0.6	—	—	—	—	—	
70	0.1	0.3	—	—	—	—	—	50	0.2	0.4	—	—	—	—	—	
69	0.2	0.4	—	—	—	—	—	52	0.1	0.2	—	—	—	—	—	
68	0.4	0.7	—	—	—	—	—	56	0.2	0.5	—	—	—	—	—	
65	0.2	0.4	—	—	—	—	—	58	0.2	0.5	—	—	—	—	—	
63	0.3	0.7	—	—	—	—	—	61	0.2	0.5	—	—	—	—	—	
62	0.3	0.6	—	—	—	—	—	63	0.3	0.6	—	—	—	—	—	
53	0.2	0.4	—	—	—	—	—	66	0.3	0.5	—	—	—	—	—	
67	0.3	0.7	—	—	—	—	—	66	0.3	0.5	—	—	—	—	—	
106	—	—	—	0.2	—	—	—	77	—	—	—	—	0.3	—	—	
105	—	—	—	0.6	—	—	—	93	—	—	—	—	0.5	—	—	
107	—	—	—	0.8	—	—	—	93	—	—	—	—	0.4	—	—	
111	—	—	—	0.7	—	—	—	94	—	—	—	—	0.3	—	—	
113	—	—	—	0.8	—	—	—	94	—	—	—	—	0.8	—	—	
112	—	—	—	0.4	—	—	—	96	—	—	—	—	0.9	—	—	
120	—	—	—	—	—	1.3	—	100	—	—	—	—	—	—	1.0	
108	—	—	—	0.5	—	—	—	107	—	—	—	—	0.3	—	—	
123	—	—	—	—	—	0.7	—	108	—	—	—	—	—	—	0.5	
125	—	—	—	—	—	0.9	—	108	—	—	—	—	—	—	0.4	

TABLE 6.—Resistance to Torsion of Nonfractured and Fractured Ulnas—Continued

Rabbit	Nonfractured Ulna								Days Required for Healing	Fractured Ulna							
	Weight Added, Gm.									Weight Added, Gm.							
	0 to 10	0 to 20	20 to 40	40 to 60	60 to 80	80 to 100	40 to 90	0 to 10		0 to 20	20 to 30	30 to 40	40 to 60	60 to 80	80 to 100	40 to 90	
	Torsion, Degrees									Torsion, Degrees							
124	—	—	—	—	—	—	0.8	113	—	—	—	—	—	—	—	0.3	
119	—	—	—	—	—	—	0.5	113	—	—	—	—	—	—	—	0.7	
122	—	—	—	—	—	—	1.0	114	—	—	—	—	—	—	—	1.0	
121	—	—	—	—	—	—	0.8	114	—	—	—	—	—	—	—	1.2	
110	—	—	—	0.5	—	—	—	115	—	—	—	—	0.3	—	—	—	
109	—	—	—	0.4	—	—	—	125	—	—	—	—	0.5	—	—	—	
117	—	—	—	0.5	—	—	—	125	—	—	—	—	0.6	—	—	—	
118	—	—	—	—	—	—	0.9	131	—	—	—	—	—	—	—	0.7	
114	—	—	—	—	—	—	0.5	135	—	—	—	—	—	—	—	0.5	
115	—	—	—	—	—	—	0.4	135	—	—	—	—	—	—	—	0.5	
116	—	—	—	—	—	—	1.8	138	—	—	—	—	—	—	—	0.8	
134	—	—	—	—	—	—	0.7	139	—	—	—	—	—	—	—	0.4	
137	—	—	—	—	—	—	0.7	140	—	—	—	—	—	—	—	0.3	
135	—	—	—	—	—	—	0.6	140	—	—	—	—	—	—	—	0.4	
133	—	—	—	—	—	—	0.8	145	—	—	—	—	—	—	—	1.9	
132	—	—	—	—	—	—	0.4	145	—	—	—	—	—	—	—	0.4	
131	—	—	—	—	—	—	0.8	152	—	—	—	—	—	—	—	0.5	
126	—	—	—	—	—	—	1.1	188	—	—	—	—	—	—	—	2.5	
130	—	—	—	—	—	—	0.7	188	—	—	—	—	—	—	—	0.5	
136	—	—	—	—	—	—	0.9	189	—	—	—	—	—	—	—	0.9	
129	—	—	—	—	—	—	2.2	189	—	—	—	—	—	—	—	0.7	
123	—	—	—	—	—	—	1.2	191	—	—	—	—	—	—	—	0.5	
127	—	—	—	—	—	—	0.9	191	—	—	—	—	—	—	—	0.5	

for the group of nonfractured ulnas and the regression line are included in figure 4.

This regression line was then considered as the base line, and the degrees of torsion of the nonfractured ulna were plotted against the days the rabbit lived after the operation (fig. 5 *A*). It was again considered as the base line in figure 5 *B*, in which the degrees of torsion of the fractured ulna were plotted against the days the rabbit lived after the operation. A curve was drawn and smoothed through the means as computed for ten day intervals. This would indicate that the fractured bone regained normal resistance to torsion approximately sixty days after fracture.

#### BENDING

The data obtained in measuring resistance to bending are given in table 7. The analysis of these data was made in a manner similar to that of the analysis of the data for torsion. Here also the weights added were not the same in each experiment. It was obvious that a straight line could be fitted well to the data for the nonfractured ulna. This was done by calculating the regression line for these data. The regression line and a scattered diagram of the data are shown in figure 6.

As in the analysis of the data for torsion, this regression line was considered as the base line, and the degrees of bending of the nonfractured ulna were plotted around it against the days the rabbit lived

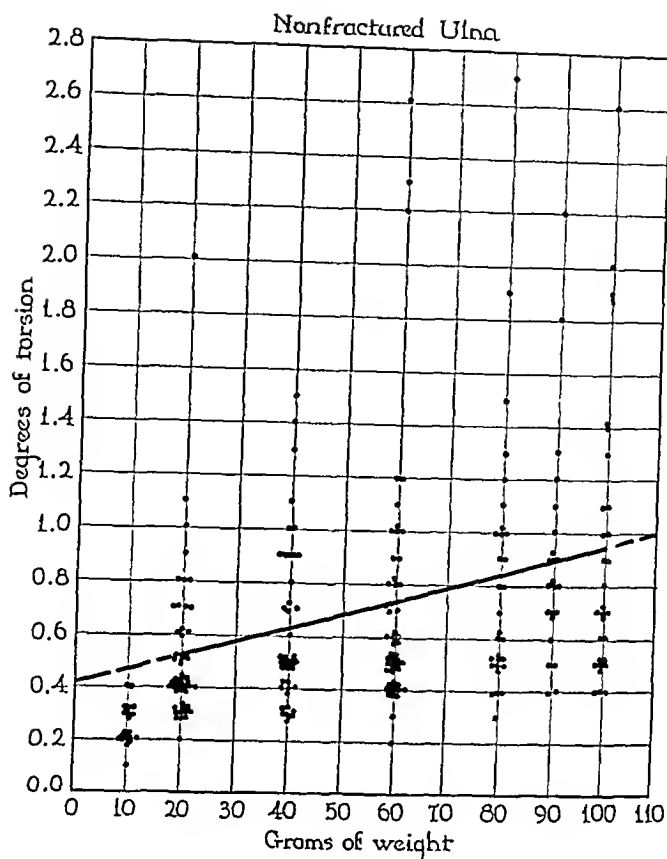


Fig. 4.—Graph for resistance to torsion in the nonfractured ulna. The regression line was computed after excluding the data obtained on addition of the first 10 Gm. of weight (formula:  $DT$  [degrees of torsion]  $= 0.4316 + 0.0053 W$  [weight]).

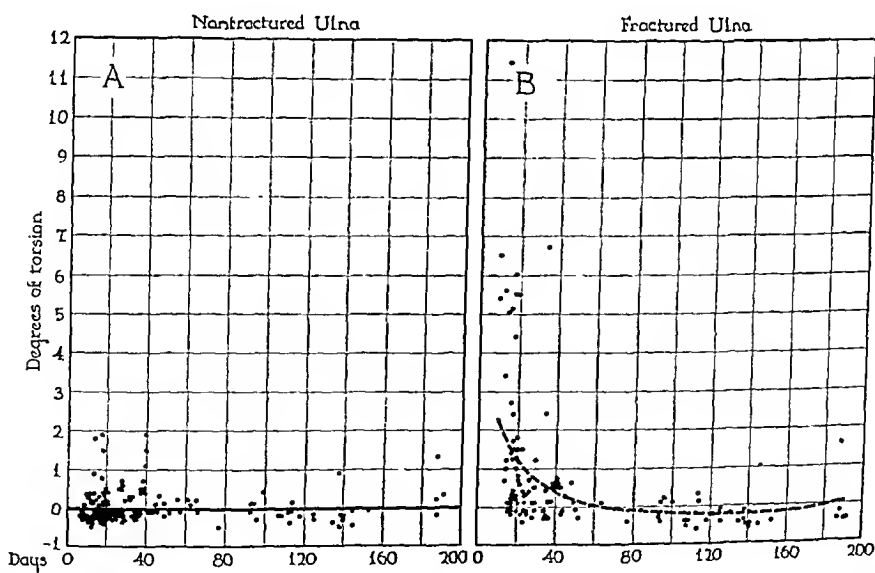


Fig. 5.—*A*, graph for resistance to torsion in the nonfractured ulna, plotted around the regression line of figure 4 as the base line (formula:  $DT = 0.4136 + 0.0053 W$ ). *B*, graph for resistance to torsion in the fractured ulna, plotted around the regression line of figure 4 as the base line. The smoother point-to-point curve is through the means computed for ten day intervals.

TABLE 7.—Resistance to Bending of Nonfractured and Fractured Ulnas

Rabbit	Right Nonfractured Ulna						Days Required for Healing	Left Fractured Ulna								
	Weight Added, Gm.							Weight Added, Gm.								
	0 to 500	480.5 to 980.5	500 to 1,000	1,000 to 1,500	1,500 to 2,000	2,000 to 2,500		2,500 to 3,000	0 to 500	480.5 to 980.5	500 to 1,000	1,000 to 1,500	1,500 to 2,000	2,000 to 2,500	2,500 to 3,000	
			Torsion, Degrees								Torsion, Degrees					
101	—	—	0.5	0.8	1.4	3.0	2.5	8	—	—	Too weak	—	—	—	—	
98	—	—	6.0	4.0	4.0	3.0	2.5	9	—	—	2.5	22.5	63.0	65.0	—	
99	—	—	1.2	4.3	2.7	2.0	2.0	11	—	—	25.0	43.0	36.0	—	—	
100	—	—	3.5	3.3	2.2	2.6	3.2	12	—	—	16.0	21.0	35.0	—	—	
83	—	—	0.5	0.5	1.1	1.1	1.8	13	—	—	3.0	12.0	55.0	—	—	
17	—	—	10.1	6.7	—	—	—	14	—	—	Too weak	—	—	—	—	
85	—	—	2.0	1.5	2.5	1.7	2.3	15	—	—	12.5	17.0	15.0	—	—	
84	—	—	1.5	1.4	0.8	1.7	2.1	16	—	—	9.0	17.5	31.5	—	—	
28	—	—	1.0	1.0	1.0	1.0	—	17	—	—	3.0	2.0	7.0	—	—	
74	—	—	1.5	0.7	2.0	2.7	5.8	17	—	—	10.0	34.0	55.0	—	—	
88	—	—	1.0	1.0	1.2	—	—	17	—	—	9.0	30.5	83.0	—	—	
5	—	—	1.2	—	—	—	—	17	—	—	—	—	—	—	—	
78	—	—	—	2.0	1.5	1.0	1.5	17	—	—	22.0	20.0	26.0	—	—	
22	—	—	4.0	5.0	4.0	—	—	18	—	—	6.0	11.5	—	—	—	
19	—	—	2.0	3.0	1.5	—	—	20	—	—	—	—	—	—	—	
60	—	—	—	—	—	—	—	20	—	—	8.0	8.5	8.5	9.0	12.0	
15	—	—	1.6	1.1	—	—	—	21	—	—	—	—	—	—	—	
55	—	—	1.3	3.4	2.6	1.2	3.8	21	—	—	—	—	—	—	—	
48	—	—	1.0	1.0	1.0	1.0	1.0	21	—	—	—	—	—	—	—	
93	—	—	0.5	0.7	0.8	—	—	23	—	—	—	—	—	—	—	
91	—	—	0.8	1.0	1.0	—	—	23	—	—	2.2	5.2	4.5	—	—	
92	—	—	1.5	1.2	1.4	—	—	23	—	—	—	0.6	1.2	1.0	—	
94	—	—	3.9	2.2	5.1	—	—	24	—	—	3.6	6.1	6.0	—	—	
95	—	—	0.4	—	—	—	—	25	—	—	1.8	3.2	3.3	—	—	
25	—	—	1.2	—	—	—	—	26	—	—	3.2	4.3	—	—	—	
2	—	—	—	—	—	—	—	27	—	—	3.2	—	—	—	—	
82	—	—	2.3	—	—	—	—	28	12.8	—	8.3	—	—	—	—	
31	—	—	2.0	0.4	2.8	0.8	3.0	29	—	—	2.3	2.4	—	—	—	
30	—	—	0.8	1.0	1.0	1.1	0.9	29	—	—	—	—	—	—	—	
81	—	—	0.5	—	—	—	—	29	—	—	—	5.0	12.0	30.0	46.0	
57	—	—	1.3	—	—	—	—	30	—	—	8.8	—	—	—	—	
1	—	—	5.8	—	—	—	—	31	—	—	2.1	—	—	—	—	
77	—	—	0.2	1.0	2.0	2.0	—	33	—	—	—	—	—	—	—	
76	—	—	1.1	3.1	3.3	—	—	34	—	—	1.5	1.8	1.7	1.8	—	
73	—	—	2.2	2.0	1.0	—	—	34	—	—	—	0.7	0.8	3.0	—	
72	—	—	1.2	—	—	—	—	36	—	—	1.3	1.0	2.0	—	—	
71	—	—	1.3	—	—	—	—	37	—	—	2.4	2.6	—	—	—	
23	—	—	3.0	1.8	1.7	2.0	—	38	—	—	1.4	1.1	—	—	—	
20	—	—	0.5	1.5	3.0	2.0	—	39	—	—	0.5	3.0	4.5	10.0	—	
90	—	—	1.0	—	—	—	—	40	—	—	5.0	6.0	8.5	6.5	—	
102	—	—	1.5	—	—	—	—	42	—	—	2.4	—	—	—	—	
89	—	—	2.0	—	—	—	—	43	—	—	1.4	—	—	—	—	
24	—	—	1.2	—	—	—	—	45	—	—	2.0	—	—	—	—	
60	—	—	1.2	—	—	—	—	46	—	—	1.0	—	—	—	—	
79	—	—	2.0	—	—	—	—	47	—	—	1.7	—	—	—	—	
70	—	—	2.7	—	—	—	—	49	—	—	4.9	—	—	—	—	
69	—	—	2.1	—	—	—	—	50	—	—	1.5	—	—	—	—	
68	—	—	2.0	—	—	—	—	52	—	—	1.6	—	—	—	—	
63	—	—	1.9	—	—	—	—	56	—	—	1.2	—	—	—	—	
62	—	—	1.7	—	—	—	—	58	—	—	2.3	—	—	—	—	
53	—	—	1.3	—	—	—	—	61	—	—	2.0	—	—	—	—	
67	—	—	2.0	—	—	—	—	63	—	—	1.8	—	—	—	—	
103	—	—	3.0	—	—	—	—	66	—	—	3.4	—	—	—	—	
105	—	—	1.5	—	—	—	—	66	—	—	2.0	—	—	—	—	
107	—	—	2.5	—	—	—	—	77	—	3.5	—	—	—	—	—	
111	—	—	1.5	—	—	—	—	93	—	—	—	—	—	—	—	
113	—	—	2.5	—	—	—	—	93	—	3.0	—	—	—	—	—	
112	—	—	2.8	—	—	—	—	94	—	1.3	—	—	—	—	—	
120	—	—	4.0	—	—	—	—	94	—	7.0	—	—	—	—	—	
108	—	—	3.5	—	—	—	—	96	—	4.6	—	—	—	—	—	
123	—	—	0.7	—	—	—	—	100	—	1.5	—	—	—	—	—	
125	—	—	0.5	—	—	—	—	107	—	3.5	—	—	—	—	—	
124	—	—	0.5	—	—	—	—	108	—	1.5	—	—	—	—	—	
119	—	—	0.5	—	—	—	—	108	—	2.0	—	—	—	—	—	
123	—	—	2.5	—	—	—	—	113	—	3.5	—	—	—	—	—	
	—	—	—	—	—	—	—	112	—	1.0	—	—	—	—	—	
	—	—	—	—	—	—	—	114	—	1.0	—	—	—	—	—	

TABLE 7.—Resistance to Bending of Nonfractured and Fractured Ulnas—Continued

Rabbit	Right Nonfractured Ulna							Days Required for Healing	Left Fractured Ulna						
	Weight Added, Gm.								Weight Added, Gm.						
	0 to 500	480.5 to 980.5	500 to 1,000	1,000 to 1,500	1,500 to 2,000	2,000 to 2,500	2,500 to 3,000		0 to 500	480.5 to 980.5	500 to 1,000	1,000 to 1,500	1,500 to 2,000	2,000 to 2,500	2,500 to 3,000
	Torsion, Degrees								Torsion, Degrees						
121	—	1.5	—	—	—	—	—	114	—	3.0	—	—	—	—	—
110	—	2.0	—	—	—	—	—	118	—	2.0	—	—	—	—	—
109	—	4.5	—	—	—	—	—	125	—	4.0	—	—	—	—	—
117	—	1.0	—	—	—	—	—	125	—	2.5	—	—	—	—	—
118	—	1.0	—	—	—	—	—	131	—	1.0	—	—	—	—	—
114	—	2.3	—	—	—	—	—	135	—	4.0	—	—	—	—	—
115	—	1.5	—	—	—	—	—	138	—	1.8	—	—	—	—	—
116	—	1.5	—	—	—	—	—	138	—	6.0	—	—	—	—	—
134	—	1.3	—	—	—	—	—	139	—	1.5	—	—	—	—	—
137	—	1.2	—	—	—	—	—	140	—	6.3	—	—	—	—	—
135	—	2.4	—	—	—	—	—	140	—	2.0	—	—	—	—	—
133	—	0.6	—	—	—	—	—	145	—	4.0	—	—	—	—	—
132	—	2.5	—	—	—	—	—	145	—	2.0	—	—	—	—	—
131	—	1.0	—	—	—	—	—	152	—	2.8	—	—	—	—	—
126	—	0.8	—	—	—	—	—	155	—	5.3	—	—	—	—	—
130	—	2.8	—	—	—	—	—	158	—	3.1	—	—	—	—	—
136	—	3.4	—	—	—	—	—	159	—	3.0	—	—	—	—	—
129	—	2.0	—	—	—	—	—	159	—	4.0	—	—	—	—	—
128	—	2.5	—	—	—	—	—	191	—	2.5	—	—	—	—	—
127	—	1.5	—	—	—	—	—	191	—	1.3	—	—	—	—	—

TABLE 8.—Means of Weight of Bone for Nonfractured and Fractured Ulnas

Nonfractured Ulna		Fractured Ulna			Difference $\pm$ Standard Error	R	P
Number of Cases	Mean $\pm$ Standard Error, Degrees	Number of Cases	Duration of Healing, Days	Mean $\pm$ Standard Error, Degrees			
67	1.6955 $\pm$ 0.0399	64	20-200	1.9588 $\pm$ 0.0501	-0.2633 $\pm$ 0.0640	4.11	>0.00

TABLE 9.—Regression Coefficients of Weight of Bone and Time of Healing for Nonfractured and Fractured Ulnas

Nonfractured Ulna		Fractured Ulna			Difference $\pm$ Standard Error	R	P
Number of Cases	b $\pm$ Standard Error	Number of Cases	Duration of Healing, Days	b $\pm$ Standard Error			
67	0.0015 $\pm$ 0.0006	64	20-200	0.0013 $\pm$ 0.0008	0.0002 $\pm$ 0.0010	0.20	0.84

after the operation (fig. 7 A). It was again considered as the base line in figure 7 B, in which the degrees of bending of the fractured ulna were plotted against the days the rabbit lived after the operation. A curve was drawn and smoothed through the means as computed for twenty day intervals of healing. This would indicate that the fractured bone had regained normal resistance to bending approximately sixty days after fracture.

## WEIGHT OF THE BONE

The data for the weight of the bones are included in table 1 with the data for tensile strength. Figure 8B is a scatter diagram of the data for the weight of the nonfractured ulna plotted against time; the regression line is also shown. It is to be noted that, although there was a great variation in the weight of the bone, there was a progressive increase in weight as the interval between the operation and the killing of the animal was increased. This was probably due to normal growth of the ulna.

Figure 8B is a similar diagram of the data for the fractured ulna and the regression line. It is evident that the fractured ulna was

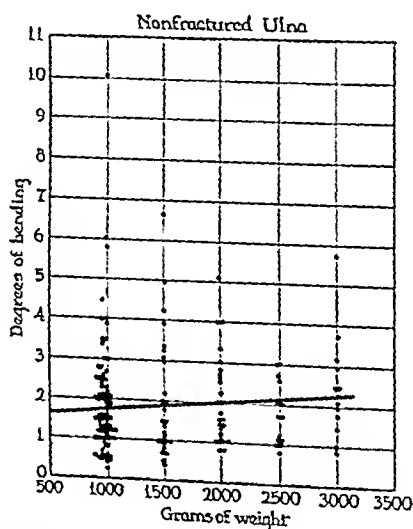


Fig. 6.—Graph for resistance to bending in the nonfractured ulna, with regression line (formula:  $DB$  [degree of bending]  $= 1.7254 + 0.00016 W$  [weight]).

increased in weight (table 8). There were probably two factors involved in this increase in weight. In the animals killed within the first two or three weeks after the operation this increase was due, either in part or entirely, to callus at the site of the fracture. Later, the callus was, at least in part, absorbed, but synostosis with the ulna was present in most of these healed fractures. In removing the bone this synostosis was cut close to the radius, leaving all the synostoses with the ulna; perhaps at times even a chip of cortex of the radius was left attached to the ulna. In spite of these different factors, the increase in weight with time was so similar to the increase in the unfractured ulna that when their constants are compared no significant difference is demonstrated (table 9).

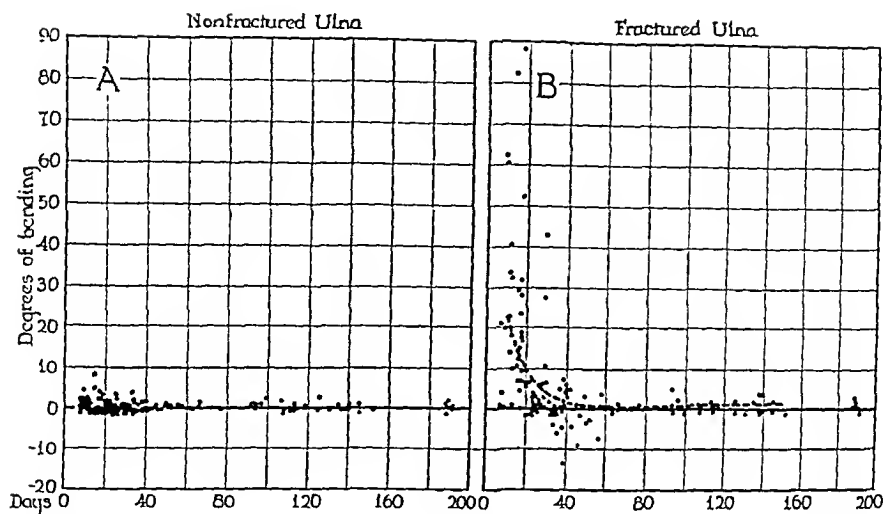


Fig. 7.—*A*, graph for resistance to bending in the nonfractured ulna, plotted around the regression line of figure 6 as the base line (formula:  $DB = 1.7254 + 0.00016 W$ ). *B*, graph for resistance to bending in the fractured ulna, plotted around the regression line of figure 6 as the base line. The smoothed point-to-point curve is through the means computed for twenty day intervals.

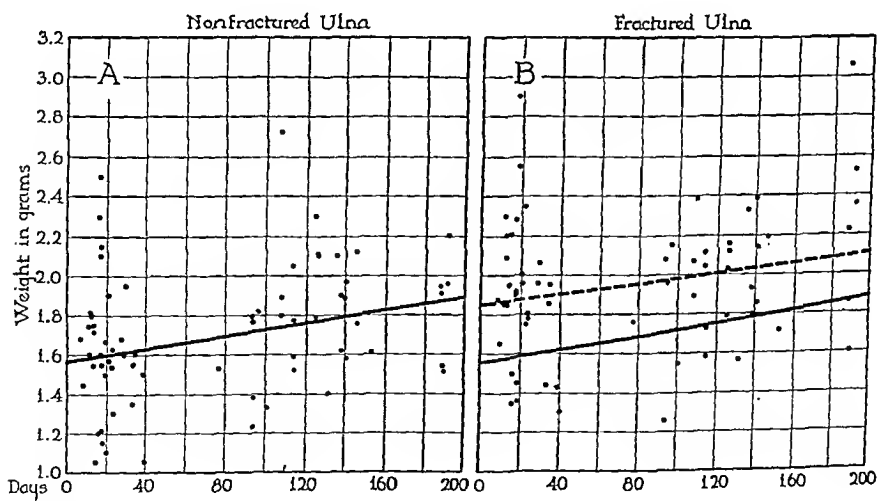


Fig. 8.—*A*, graph for weight of the nonfractured ulna, with the regression line (formula:  $BW [\text{weight of the bone}] = 1.5852 + 0.0015 D$ ). *B*, graph for weight of the fractured ulna, with regression line (broken line) for these data (formula:  $BW = 1.8616 + 0.0013 D$ ) and the regression line for the nonfractured ulna (unbroken line).

## COMMENT

The data analyzed as measures of torsion and bending were obtained by adding weights and taking a reading after the addition of each weight. Readings were also taken as these weights were removed. The data for torsion were analyzed and found to fit well to a straight line, but not as well as the data obtained on the addition of weight. This difference may be due to a third factor, time, which was disregarded in the experiment. Bone obviously has imperfect elasticity and would therefore show a lag in torsion or bending on the addition of weight and perhaps return more slowly after the removal of weight. To correct for this, it would be advisable, in collecting additional data, to take the reading at a constant interval after the addition or removal of weight.

As has been stated, partial correlation between the tensile strength of the nonfractured ulna, weight and time was made to determine what part increase of weight played in the observed increase in tensile strength. The coefficient of correlation was 0.0542, which is not significant; moreover, the standard errors of the array for tensile strength alone and with weight, time and both time and weight held constant were determined. With  $\sigma$  denoting the standard deviation, they are as follows:

Tensile Strength	Standard Error
$\sigma$ Tensile strength .....	$10.90 \pm 0.95$
$\sigma$ Tensile strength .....	$10.90 \pm 0.95$
$\sigma$ Tensile strength—time.....	$8.46 \pm 0.74$
$\sigma$ Tensile strength—time—weight.....	$8.44 \pm 0.96$

From these figures it is evident that the standard error of tensile strength is approximately the same, whether weight is held constant or not, but if time is held constant it is changed by approximately 22 per cent. This indicates that the increased tensile strength in the nonfractured ulna (fig. 1 A) is due to physical or chemical changes in the bone that occur with age rather than to increased weight of the bone.

In rechecking these experiments it is proposed to select animals which will have reached approximately the same age at the time they are killed.

## SUMMARY AND CONCLUSION

1. It is important to determine the normal rate of healing in bone and its variability before any attempt is made to estimate possible variations.
2. In determining the return of function or strength in healing bone three factors were measured, i. e., tensile strength, resistance to torsion and resistance to bending.
3. The ulna of the nonfractured leg was used as a control.



4. So far as tensile strength is concerned, healing was complete approximately thirty days after fracture in the ulna of the rabbit, but within the limits of this experiment the fractured bone never completely regained the tensile strength present in normal bone of the opposite leg.

5. The fractured ulna of the rabbit was found to have completely regained its resistance to torsion and bending approximately sixty days after fracture.

# AMBULATORY TREATMENT OF VARICOSE STATE BY COMBINED LIGATION AND THROMBOSIS BY INJECTION

A STUDY IN END-RESULTS

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The results obtained at the Stanford University Clinics following therapeutic thrombosis of varicose veins by the injection of sclerosing solutions were reported in 1931.<sup>1</sup> Careful examination a year or more following thrombosis disclosed recanalization or recurrence in the thrombosed veins in 98 per cent of all patients examined. In spite of the recurrence of varicosities and recanalization of veins, 54 per cent of the patients had complete relief of all symptoms attributed to the presence of the varicosities and 94 per cent obtained partial or complete relief of symptoms during the period of observation. That the recurrence was due to recanalization of the thrombus, and not to the formation of new veins or enlargement of collateral venous channels, was shown by a microscopic study of veins excised at intervals following thrombosis by injection, and by personal observation and comparison of the recurrent varicose veins with the charted positions of the original varicosities. At that time it was suggested that the venous back pressure in the unthrombosed upper saphenous segment might be the chief contributing factor in the rapid recanalization and recurrence of the thrombosed veins, and that the thrombosis caused by the injection of sclerosing agents might well be supplemented by the proximal ligation of the saphenous vein at the fossa ovalis, a procedure first suggested as a means of preventing recurrence by de Takáts.<sup>2</sup>

Since 1930 my associates and I have endeavored to persuade patients who seek relief from varicosities for other than cosmetic reasons (a number of women with small single dilated veins apparent through sheer hosiery seek cosmetic relief only) to have high ligation of the saphenous vein with injection and thrombosis of the veins distal to the point of ligation.

The patients chosen for the combined ligation and injection had tortuous, moderate to large varicosities, and with one exception each

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1. Howard, Nelson J.: Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection, *Arch. Surg.* 22:353 (March) 1931.

2. de Takáts, Géza: Ambulatory Ligation of the Saphenous Vein, *J. A. M. A.* 94:1194 (April 19) 1930.

patient suffered from symptoms directly attributable to the varicose state. The exception was a woman of 29 whose varicosities became apparent at the age of 14 and grew progressively larger until the distended veins became a distressing sight, although they produced no symptoms. Before proceeding with the ligation and injection, each patient underwent a thorough general physical examination; the blood pressure, urinalysis, differential white blood cell count and hemoglobin determination were recorded, and blood was taken for a Wassermann test. As in the previous study of treatment by injection alone, particular information with regard to the varicose veins was recorded on a separate chart. The position of the varices, their relative size and the competency of the valves of the saphenous and perforating veins were determined by the Trendelenburg and walking tourniquet tests. In instances in which the patency of the deep veins was questionable, tight pressure bandages worn for a week with relief afforded adequate evidence of patency in the deep veins of the leg.

#### METHOD

Previous to ligation the course of the saphenous vein, if not visible in the upper part of the thigh, was traced to the region of the fossa ovalis by palpation of the impulse transmitted on percussion. Under local anesthesia and through a transverse incision at the selected site of operation the saphenous vein was exposed and freed of surrounding areolar tissue. Unnecessary trauma to the vein was avoided. The vein was doubly ligated with ligatures of medium black silk, placed about 1 cm. apart. The ligatures were left long, so that after cutting between them they might be used as traction sutures. The proximal stump was transfixated and tied distal to the ligature, for it was evident from observations made at operation that coughing or increasing intra-abdominal tension markedly ballooned out the freed proximal stump. The respiratory venous excursions were readily observed. Failure to transfix as well as to ligate the proximal stump almost caused a fatality in one case. The ligature blew off under exertion and, following the resultant hemorrhage, the patient had a pulmonary embolus. It is important to tie and transfix the proximal stump without trauma from clamps or forceps that might lead to a propagated thrombus of the proximal stump. With the distal stump of the saphenous vein held taut by means of the long ligature, from 10 to 20 cc. of 20 per cent solution of sodium chloride was injected in a centrifugal direction. The vein was again tied to prevent the escape of the hypertonic solution into the tissues, and the wound was closed with interrupted sutures of fine black silk in the subcutaneous tissues and the edges of the skin and covered with sterile dressings. I have found it advisable to flush the wound with physiologic solution of sodium chloride before closure, immediately after injection of the sclerosing agent. Frequent postoperative inspections of the wound and dressings are necessary, for it is difficult to maintain dressings satisfactorily in the region of the groin, especially when the patient is ambulant. Sutures of the skin were removed in from five to seven days.

This procedure was carried out in the outpatient clinic by resident members of the surgical house staff. The patients were all ambulatory, and returned to their work or to their homes the day of the operation. It was usual to wait for the healing of the wound and removal of the stitches in the skin before proceeding to obliterate the remaining patent veins by injection of the thrombosing solution.

Injectations were continued until all visible and palpable superficial veins were well thrombosed. Several instances of almost complete thrombosis of veins distal to the ligation occurred following the single injection, but in only one case was it so complete as to render further injections unnecessary. Patients with varicose ulcers were first treated by injection and application of a boot of Unna's paste until the small ulcers had healed or the larger ulcers were relatively clean and free from inflammation in the surrounding tissues before the ligation and further injections were attempted.

From May 1930 to February 1932, ninety-one ligations and injections were done on 68 patients in the outpatient clinic. Twenty-three of the ligations were bilateral. We were able to reexamine and question as to symptoms 58 patients, of whom 21 had both saphenous veins ligated. Since each set of varicosities is liable to recanalization and reproduction of signs or symptoms, it might be well for statistical purposes to list the observations by ligations rather than by patient. From this standpoint 86.8 per cent of the results were reexamined a year or

TABLE 1.—*Classification of Results of Treatment According to Appearance of Symptoms and Signs*

Classification	Recanalization	Percentage
—0	Complete recurrence to original size.....	5
—1	Visible as varicosities smaller than original.....	29
—2	Visible straight veins or visible isolated segments.....	37
—3	Not visible; palpable and percussable as patent; blood easily withdrawn from lumen .....	32
—4	Not visible; barely palpable as patent; aspiration of blood necessary to prove recanalization .....	1

more after ligation and thrombosis by injection. We were able to demonstrate recanalization in 100 per cent. The patency of the lumen of the vein is easily demonstrated by the transmission of a palpable impulse along the vein on percussion with the finger, and a Luer syringe with an intravenous needle serves to withdraw blood easily from the lumen of the vein.

The recanalization of the veins does not mean that the veins have recurred as varicosities. From the beginning of the following study the results were classified, on reexamination of the patient, in the following manner: —0, complete recanalization of the veins and recurrence of the varicosities to the original size; —1, the veins completely recanalized and visible as definite varicosities, yet smaller than the original veins; —2, visible straight veins, or isolated visible varicose segments and the varicose system as a whole recanalized, as shown by the aforementioned tests; —3, the original thrombosed varicosities not visible, but palpable and percussable as patent, and proved recanalized by the withdrawal of blood from the lumen with a syringe and needle; —4, barely palpable and percussable as patent but needing the final proof of withdrawal of blood from the lumen of the vein to prove recanalization. In table 1 the end-results are summarized in the foregoing manner. It is apparent

that only 23 per cent of the patients (those in classes —0 and —1) have recanalization to the point of recurrent varicosities, and 77 per cent (classes —2, —3 and —4) are to be regarded from a cosmetic standpoint as cured at the time of reexamination. The patients in class —2 may return for reinjection of the visible vein segment. In my experience young women with such a result returned for rethrombosis of the recanalized visible vein.

Fourteen patients received quinine and ethyl carbamate (urethane) as the sclerosing agent. The results in 12 patients were no more efficient and lasting than in patients treated with 20 per cent sodium chloride. Three patients received injections of sodium morrhuate in addition to the ligation of the vein. If the experience of the clinic were confined to these patients alone, we would not be justified in drawing conclusions as to the effectiveness of quinine and ethyl carbamate or sodium morrhuate. These solutions were used at intervals to the exclusion of treatment

TABLE 2.—*Symptoms and Signs Due to Varicose State After One Year*

	Before Treatment	One Year After Treatment
Pain.....	63	3
Fatigue.....	65	6
Burning sensation.....	38	0
Hemorrhage.....	4	0
Ulceration.....	25	2
Swelling and edema.....	44	3
Eczema.....	15	1
Cramps.....	4	2

with sodium chloride in patients who received injections without ligation. A sufficient number of such patients has been observed to suggest that the efficiency of thrombosis and the duration of results are certainly not superior to those noted following the injection of hypertonic saline solution. However, they have the advantage of not causing cramps during injection.

The symptoms and signs caused by the varicose condition in this series of patients before treatment are shown in table 2. Fatigue of the lower limbs, especially on long standing, was the most frequent complaint. This condition was present in 65 patients. A dull aching pain producing discomfort was present in 63. This was distinguished from a burning sensation, present in 38 cases. Definite severe cramps in the legs, not associated with exercise, came on while at rest or during the night in 4 people. Swelling and edema of the leg and ankle were noticed in 44 cases. There were twenty-five varicose ulcers, and 4 patients had spontaneous hemorrhage. Marked pigmentation of the lower part of the leg was present in 34 patients, and in 15 an eczematous, weeping cutaneous surface was an added complication.

On follow-up examination only 12 patients complained of symptoms. Six were still prone to fatigue of the legs on long standing; 3 com-

plained of pain, and 3 still had edema of the affected leg. Two had recurrence of cramps in the legs. In 1 patient the eczematous condition had never disappeared, and a small ulcer which had been healed recurred. Another patient in whom beginning recanalization of the veins had been noted at ten months had recurrence of an ulcer at twenty-one months, although the veins were classed only as —3. Only 1 patient with bilateral ulcers in the entire group with ulcer could not be reexamined a year following treatment. Thus there are 2 known recurrences among 25 patients treated for ulcers, 23 of whom were followed up for over a year after healing. This is particularly striking, for the patients with ulcers were not requested to wear pressure bandages or elastic stockings after ligation with thrombosis of the varicosities and healing of the ulcer.

As the patient is not aware of the reopening of the lumen in the veins, one has no means of estimating the time which elapses after treatment before recanalization occurs. However, in 4 patients recanalization was noted as beginning in four months, becoming complete at seven, eleven, twelve and sixteen months as —2, —2, —3 and —3 types, respectively, of recanalization. Two patients had a definite —2 grade of recanalization at five months. In 58, or in 65.8 per cent, recanalization was noted within the first twelve months after thrombosis. In the remaining 34.1 per cent recanalization was found in the second year after treatment. No definite correlation could be found between the grade of recanalization and the number of months elapsing from the time of thrombosis. One surprising fact noted in 13 patients, reexamined after the onset of recanalization at intervals of from four to fifteen months, was the failure of the veins to recanalize to such an extent as to change the classification of their grade of recanalization.

In the previous study of the end-results from injection alone the suggestion was made that "stripping" of the saphenous veins from the femoral opening to the knee, combined with thrombosing injections into the veins of the leg might prove a more permanent means of interrupting venous back pressure and preventing or retarding the recanalizing process. Four patients consented to enter the hospital for this operation. Of the 4, 1 stopped coming to the clinic for injections after discharge from the hospital, and could not be traced for follow-up examination. In the 3 remaining patients recanalization occurred to —2, —3 and —2 in eight and one-half, eleven and one-half and eleven months, respectively. The last case, that of a barber, was particularly interesting. First treated by injection and thrombosis in March 1928, his veins had recanalized to the —2 degree in six and one-half months. Again the treatment by injection produced excellent, rapid and complete thrombosis of all superficial veins from the ankle to the saphenous opening. Each time the thrombosing process was accompanied by fairly extensive perivenous inflammation, and there

can be no question as to the completeness of the thrombosis. In seventeen months the veins had again recanalized and this time they were as large as before any treatment, a —0 result, accompanied by tiredness, aching of the legs and recurrence of an ulcer healed for almost two years. A stripping operation was performed in the hospital during May 1930, at which time the veins below were completely thrombosed by injection. Perivenous inflammation in both calves again was marked, accompanied by tenderness and local induration along the channel left by the stripped vessels. In eleven months recanalization of the thrombosed vessels to the —2 degree had occurred, and a new vein had formed in the thigh from the saphenous opening to the region of the popliteal fossa. At operation the saphenous vein and the superficial circumflex iliac, superficial epigastric and superficial external pudendal veins, all tributaries at the saphenous opening, had been ligated and cut across.

The most serious complication that occurred in this operative series was a nonfatal pulmonary embolism in the patient referred to in the description of the technic of ligation, whose proximal saphenous stump was not transfixed as well as tied for additional security. This patient climbed four flights of stairs, and, under this exertion, the ligature blew off. The patient fainted from loss of blood and was taken to the city emergency hospital where a pressure pack bandage was applied. Secondary bleeding occurred and the patient later experienced a sudden thoracic pain followed by bloody expectoration and pleural pain with a friction rub. Rest in bed and careful nursing probably prevented the occurrence of a more serious embolic phenomenon.

#### CONCLUSIONS AND COMMENT

This experience is a blow to the hopes that ligation with injection might prevent recanalization of the thrombosed veins, or prevent recanalization to the extent of recurrence of the varicose veins. While recanalization could be demonstrated in 100 per cent of the patients reexamined from twelve to twenty-four months after treatment, it is particularly encouraging that in only 23 per cent had the condition advanced to the point of return of visible dilated veins or varicosities, and 77 per cent might still be considered cured from a cosmetic standpoint. Symptoms remained or recurred in only 12 patients, or 15 per cent of those reexamined. The treatment has been particularly effective in persons with ulceration or with the varicose type of eczema. Two ulcers recurred, and 1 patient (with an ulcer) failed to be relieved of the eczematous condition of the skin. Thirteen patients were followed up from four to fifteen months after recanalization had occurred. The recanalization did not progress to continued enlargement of the lumen of the vein. This is in marked contrast to my

experience with injection alone, for when recanalization was present, reinjection was considered necessary within from two to six months.

The 4 patients on whom the stripping operation and injection were done did not show better results than those with ligation and injection, and since the operative trauma is greater and hospitalization and general anesthesia are necessary, this method cannot be recommended or advised unless one completes the radical operation by excision of the saphenous system below the lowest stripped segment.

Wherever systematic follow-up studies have been carried out, based on personal reexamination rather than on returns from questionnaires, the results are in close agreement as to the return of varicosities following adequate thrombosis by injection, as well as in the observation that such return is not necessarily followed immediately by subjective symptoms. Outstanding among such follow-up observations are those of Svend Hansen, of Karsten Kettel and of Faxon. In 107 patients with uncomplicated varicose veins, Svend Hansen<sup>3</sup> reported good results in 35 per cent, with recurrence in 49 per cent and no improvement in 16 per cent from one to three years after treatment. The observations of Kettel<sup>4</sup> were particularly striking since they were carried out on a relatively large group of follow-up examinations (225) over a longer time (one to five years) than other reported results. He found that after one year 91.5 per cent of his patients with uncomplicated varicosities were free from symptoms (94.5 per cent free at the completion of treatment), and one third of the group reexamined had recurrences of varicosities. The percentage of recanalization was not observed. Kettel further found that as time elapses the number of patients without symptoms decreases. Thus, at the end of five years following treatment only 13 (28 per cent) of 45 patients examined had remained free of symptoms; 15 (33 per cent) were still improved and in 17 (38 per cent) the results were considered poor. These figures are for subjective findings. As to the objective return of varicose veins or complications Kettel classified the results as good, improved or poor. With this classification and considering both the "improved" and the "poor" results as showing objective evidence of the return of varicosities or dilated visible veins the incidence of recurrence for the five years of observation of uncomplicated varicose veins thrombosed by injection is as follows: first year, 38.5 per cent; second year, 65.6; third year, 64.8 per cent; fourth year, 79.5 per cent, and fifth year, 86.6 per cent. The group of patients whose varicosities were complicated by ulceration or eczema (131 with ulcers and 8 with eczema) offered the crucial test for the effi-

3. Hansen, Svend: *Injektionsbehandlung von Varicen und ihre Resultate*, Arch. f. klin. Chir. 166:527, 1931.

4. Kettel, Karsten: *Zur Injektionstherapie der Krampfadern: Augenblickliche Resultate; Nachuntersuchungen*, Beitr. z. klin. Chir. 154:585, 1932.



ciency and permanency of the treatment by injection. Of these 139 cases, Kettel was able to follow up 102. At the completion of the treatment 72 of the ulcers were healed, 9 were smaller and 13 uninfluenced by the therapy. Of the 72 healed ulcers 52 had remained healed when examined from one to five years after treatment, but 9 patients found it necessary to wear compression bandages, for otherwise the skin tended to break down. Thus, 43 of the 72 patients were able, from one to five years after treatment, to continue their usual occupations unhampered by compressive bandages or the necessity of continuous medical treatment for chronic ulcers of the legs. Of the 8 patients with varicose eczema only 1 was healed, 1 improved and 6 showed no change in their condition over a three year period of observation.

Every physician has the memory from student days of patients with ulcers of the leg older than the student, the wounds having been dressed by a continuous succession of interns, house officers and residents beyond the memory of the oldest physician of the clinic. With such memories the results of Kettel are in overwhelming contrast.

Faxon,<sup>5</sup> at the Massachusetts General Hospital, followed approximately half of 613 patients treated by injection. In a careful and candid survey of the results at an average of one and one-fourth years after the completion of treatment, he found that there were recurrences of varicose veins in 63 per cent of the 314 patients followed up. New varicosities developed in 25 per cent of the cases, which is higher than in my own experience and observations. The findings of Faxon also show that the patient's appreciation is often greater than the objective evidence warrants, for 59 per cent were enthusiastic, 34 per cent moderately pleased and only 7 per cent disappointed in the results. Of the patients having symptoms referable to the varicose state, 38 per cent were relieved of pain and 19 per cent of edema, and in 61 per cent the ulcers remained healed over the period of observation.

In the treatment by injection alone particular efforts were made to obtain permanent obliteration of the lumen of the vein by means of an efficient thrombosing agent (20 per cent solution of sodium chloride); and the following adjuncts: (1) thrombosis of the saphenous vein in the thigh (frequently ascending thrombosis to the sapheno-femoral junction was secured); (2) emptying of the vein at the time of injection by elevation to or beyond the horizontal plane with stripping of the vein by means of the finger; (3) localization of the segment of the vein in which the injection was made by means of proximal and distal tourniquets; (4) pressure bandages during and after the period of thrombosis to achieve collapse and adherence of the walls of the veins; (5) hot solutions (110 F.) to add thermal to chemical trauma,

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5. Faxon, Henry H.: End Results in the Injection Treatment of Varicose Veins, *New England J. M.* 208:357 (Feb.) 1933.

and (6) mechanical trauma by rough massage along the vein following the injection. The blame for recanalization or recurrence has been placed, particularly by McPheeters,<sup>6</sup> on the failure to observe many of the adjuncts to injection.

Since from the beginning all efforts were aimed at permanent results as well as the immediate relief of the symptoms and complications of varicosities, I have utilized the factors enumerated to further the thrombosis and lasting organization of the sclerosed veins. In spite of this, the vein responded with recanalization, the natural history of a thrombus, and, as these follow-up studies have shown, such recanalization proceeds to the extent that the varicosities recur, and the symptoms of the disease are eventually manifest. Undoubtedly this will be true of the treatment by ligation and injection as well, for my figures show the return of varicosities from this procedure within the short time of observation. I have reason to believe that this return will be slower and the development of the varicose veins and their symptoms may remain in abeyance for a longer period than with injection alone. One discrepancy between my results and those of other observers might well be explained by the fact that in the first report patients were classed as having recurrences even though the recanalized veins had not become dilated varicosities. The suggestion of Dr. Emile Holman, that recanalization should not be considered necessarily as a recurrence, is valuable, and particular attention was paid to it in the reexamination of patients in the present series. McPheeters,<sup>7</sup> too, showed that recanalization does not progress with equal rapidity along the entire course of the lumen of the vein, and that even in the presence of recanalization the actual condition may still be similar to multiple ligations along the course of the saphenous system. De Takáts'<sup>8</sup> most recent report gave only 10 per cent recurrence following treatment by ligation and injection. I feel that his admitted and pardonable failure to secure the return of the patients from the clinic for reexamination as well as the interest we have manifested in the process of recanalization explains the gross differences in the two findings.

The problem of the treatment of varicose disease has been advanced tremendously by the adoption of treatment by injection. Few physicians now consider returning to the radical operation. The purpose of evaluation of treatment by injection is not to discourage or to abandon the distinctly valuable therapeutic method, but to find its

6. McPheeters, H. O.; Merkert, C. E., and Lundblad, R. A.: Causes of Failure in Injection Treatment of Varicose Veins, *J. A. M. A.* **96**:1114 (April) 1931.

7. McPheeters, H. O., and Lufkin, N. H.: Pathological Study of Injected Varicose Veins, *Surg. Gynec. & Obst.* **54**:511, 1932.

8. de Takáts, Géza, and Quillin, Lawrence: Ligation of the Saphenous Vein, *Arch. Surg.* **26**:72 (Jan.) 1933.

limitations. The next step should be prophylactic. All varicose veins do not have a common cause. In over one third of the patients the first signs of varicosities develop in adolescent or early adult years. This group seems to have a congenital origin, and studies of the embryologic development of the valves of the veins of the extremities and of the progressive disappearance of many or all the valves in the saphenous system in the first few months of extra-uterine life suggest a clue to the development of this presumably congenital group. Endocrine factors have been mentioned, but no one has satisfactorily indicated the endocrine disturbance or separated it clearly from those of mechanical nature. It is known, however, that varicosities make their appearance following thrombophlebitis of infectious diseases, childbirth and operative procedures. Also, varicosities are known to have a definite relation to trauma of the lower extremities. Fractures, crushing injuries and osteomyelitis of the lower part of the leg are often followed by unilateral varicosities. During operative procedures for osteomyelitis or for the reduction of a fracture one may encounter thrombosed veins from which, on incision, fragments of dark thrombi may pour into the operative wound. Examination of legs amputated for crushing or infected compound injuries often reveals the venae comites as the source of interstitial hemorrhage or thrombosis far more frequently than the arteries. The posttraumatic edema of fractures of the lower part of the leg may persist for months, occasionally for two years after the removal of splints and the beginning of weight bearing.

The early and continued use of pressure bandages or elastic support of the limbs of patients with thrombophlebitis and edema is imperative whether the condition is puerperal, postoperative or traumatic.<sup>9</sup> Adequate support given the superficial saphenous venous system from the moment the patient is ambulatory not only prevents the increase of edema but should accelerate to the fullest extent the recanalization of the deep, thrombosed veins and in this way prevent or minimize the future development of varicosities in the superficial venous system.

In regard to operative ligation at or near the saphenofemoral junction followed by treatment by injection, my experience demonstrates that such a procedure does not prevent the recanalization of therapeutically thrombosed veins, but I feel that it definitely retards the

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9. It is the custom of Dr. Emile Holman to insist that patients with postoperative thrombophlebitis remain in bed until the edema subsides. The ambulatory state is then not followed by edema. Repeated trials should be made to determine when freedom from edema (with the patient ambulatory) occurs. Three months in bed is not too long a time to carry out this regimen. A woman who had bilateral postoperative thrombophlebitis with marked edema was in bed for three months in order to arrive at the ambulant edema-free state. Five years subsequently she was free from edema, had no varicosities and was able to carry on her normal mode of living.

recurrence of the varicosities. Certainly persons with massive varicosities, with incompetence of both saphenous and perforating valves and with ulceration or eczema have benefited more by ligation than by injection alone. For uncomplicated varicosities without incompetent perforating veins and without ulceration or eczema, injection alone produces an eminently satisfactory result from the patient's point of view. That such injections will require repetition over the course of years should be explained to the patient and anticipated by the physician. Injection into varicosities for cosmetic reasons alone should be carried out in early varicosities, even in young adults, so as to reduce continually or to prevent the reflex flow and stagnation that are believed responsible for the complications of the varicose state. A possible danger in this might be that veins dilated early, when thrombosed, might suffer destruction or distortion of the competent valves by the subsequent organization, so that in time the system would lend itself with greater ease to dilation by hydrostatic pressure in the upright position. I have not found this to be true so far, and in patients with competent perforating valves with definite recurrence of varicosities after injection I have not observed incompetence of perforating veins on return of the varicosities.

#### SUMMARY

1. Eighty six and eight-tenths per cent of the patients treated by ligation and injection were observed for from a year to twenty-nine months after treatment.
2. In spite of the ligation and injection, 100 per cent of these patients showed recanalization of the previously thrombosed veins.
3. In only 23 per cent was there recanalization to the extent of the return of varicosities or of visible large veins; 77 per cent of the patients could be considered cosmetically cured.
4. At the end of the period of observation symptoms remained or recurred in only 12 patients—15 per cent of those followed up or 13 per cent of the entire group treated.
5. Ligation with thrombosis by injection cannot prevent recanalization, but it retards recanalization to the point of return of varicosities, and should be used in complicated varicosities (incompetent perforating veins, ulcers and eczema).
6. Prophylaxis of varicosities should be the aim of the physician. Prolonged use of pressure bandages or elastic support should be insisted on in every case of thrombophlebitis or edema of a local circulatory nature in the lower extremities. Early uncomplicated varicosities should be treated by thrombosis by injection, repeated when recurrence of varicosities takes place in order to guard against the complications of the untreated varicose state.

# THYROID DISORDERS

## VI. THE SUPRARENAL FACTOR IN REACTIONS TO THYROIDECTOMY

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AND

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Many of the reactions characterizing the various effects of operation on patients with hyperthyroidism resemble the responses which can be produced in such patients by the subcutaneous injection of epinephrine hydrochloride. As a result of clinical studies made during the past year, which are reported here, the belief seems warranted that the suprarenal glands play an important rôle in the clinical manifestations exhibited by patients with hyperthyroidism before and during thyroidectomy. Cannon and his associates<sup>1</sup> showed by physiologic experiments that the secretion of the thyroid and the active iodine-containing compound isolated from the thyroid gland by Kendall<sup>1b</sup> sensitized the sympathetic nervous system to the action of epinephrine. These researches explain the increased sensitiveness to epinephrine exhibited by patients suffering with hyperthyroidism and form the basis of the epinephrine test (E. G.<sup>2</sup>).

Long experience in observing the responses produced by the subcutaneous administration of epinephrine hydrochloride in patients with hyperthyroidism has made us familiar with the symptoms and signs which are manifested whenever there is a sudden increase in the amount of epinephrine introduced into the circulation. Thus in the epinephrine test described by one of us (E. G.) it was found that when a dose of 0.5 cc. of 1:1,000 solution of epinephrine is injected subcutaneously into the patient with hyperthyroidism, the following signs and symptoms are produced. There occurs an early, fairly sharp rise of the systolic blood pressure and pulse rate of from 10 to 50 or more points. At the same time one finds as a rule a slight to moderate fall of the diastolic

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From the Department of Surgery, Long Island College Hospital.

Read before the American Association for the Study of Goitre, Memphis, Tenn., May 17, 1933.

1. (a) Cannon, W. B., and Cattell, McK.: *Studies on the Conditions of Activity in Endocrine Glands: III. The Influence of Adrenal Secretion on the Thyroid*, Am. J. Physiol. **41**:74, 1916. (b) Levy, R. L.: *IV. The Effect of Thyroid Secretion on the Pressor Action of Adrenin*, *ibid.* **41**:492, 1916.

2. Goetsch, E.: *Newer Methods in the Diagnosis of Thyroid Disorders: Pathological and Clinical: B. Adrenaline Hypersensitiveness in Clinical States of Hyperthyroidism*, New York State J. Med. **18**:259, 1918.

pressure. As a result, the pulse pressure, which is indicative of the work of the heart, is greatly increased. In the course of from thirty to thirty-five minutes there is a moderate fall in the systolic pressure, then a moderate secondary rise, which is succeeded by a gradual fall to the normal in about one and one-half hours. The diastolic pressure also returns to its previous level in this interval. The respirations become deeper and often moderately accelerated. Simultaneously with these changes one sees an exaggeration of the clinical picture of exophthalmic goiter or hyperthyroidism, especially the nervous manifestations. All or part of the following symptoms are to be found: increased tremor, apprehension, precordial and peripheral throbbing, and asthenia, and, in fact, an increase of any of the symptoms of which the patient may previously have complained. Vasomotor changes may be present. The initial vasoconstriction with pallor and coldness of the hands and feet is followed by vasodilatation with flushing and sweating. There may be a slight rise in temperature and a slight diuresis. Furthermore, in the past several years studies conducted in the surgical clinic of the Long Island College Hospital have shown that a striking leukocytosis occurs promptly after the subcutaneous injection of epinephrine hydrochloride in the patient with hyperthyroidism. In a paper on this subject, read before this association two years ago by one of us (E. G.), it was pointed out that the hypodermic injection of 0.5 cc. of epinephrine hydrochloride in a patient with hyperthyroidism was followed by a prompt and sharp increase in the number of leukocytes. These may increase from the normal count to 30,000 or 35,000 per cubic millimeter of blood. The differential count at this time indicated a striking mononucleosis in which there were both relative and absolute increases in the mononuclear cells. Simultaneously there occurred a striking diminution in the percentage of polymorphonuclear cells. At the end of from one to two hours, the white cell count had returned approximately to the preinjection level. Apropos of this, Menkin<sup>3</sup> pointed out that emotional stimulation in animals caused a relative increase in the mononuclears in the circulating blood. An increase in the blood sugar is also known to occur following an injection of epinephrine hydrochloride, which presumably mobilizes the glycogen in the body tissues. Incidentally, a concomitant rise in the body temperature has been noted.

Bearing in mind these various manifestations produced by the administration of epinephrine hydrochloride in the patient with hyperthyroidism, the surgeon experienced in operations on the thyroid gland could not fail to be impressed by a striking similarity in the clinical reactions of the patient with hyperthyroidism to thyroidectomy and to the admin-

3. Menkin, V.: Emotional Relative Mononucleosis, *Am. J. Physiol.* 85:489, 1928.

istration of epinephrine hydrochloride. Accordingly, we planned to study more minutely the various effects produced by thyroidectomy. Before describing in detail the operative reactions, we shall enumerate the harmful factors which are inherent in practically every major operation and which are directly or indirectly responsible for these reactions. These factors are well recognized. They are, in brief, the emotional states of fear and apprehension and the exhausting factors of pain, trauma, possible hemorrhage, metabolic and nervous strain, anesthesia and the possible anxiety, nausea, vomiting and starvation of the immediate postoperative period. It is needless to elaborate further on the nature of the major ordeal of operation, particularly on a nervous and sensitive patient. In this connection one may recollect the interesting and significant contribution of Cannon<sup>4</sup> with respect to the function of the suprarenal glands and their increased activity resulting from the emotions of fear and anger and following painful stimuli. There was produced accordingly an increased amount of epinephrine in the organism. Thereupon he elaborated his theory of the emergency function of the suprarenal medulla in pain and the major emotions. Surgeons are forever indebted to Crile<sup>5</sup> for emphasizing these noxious factors and for his technical methods of reducing their harmful effects in all operations and particularly in operations on the sensitive patient with hyperthyroidism. His technic of anoci-association has been fully described and is familiar to all.

It is our purpose to describe somewhat minutely the reactions to thyroidectomy observed in the patient with hyperthyroidism, to point out the similarity of these reactions to those previously exhibited by the same patient after a hypodermic injection of epinephrine hydrochloride and to offer what appears to be demonstrable evidence that suprarenal activity is the causative agent in the production of the characteristic operative reactions to thyroidectomy.

#### METHOD OF STUDY

The preparation of the patient and anesthesia were uniform. It has been customary to administer 1/6 grain (0.0108 Gm.) of morphine hypodermically an hour before operation and a second injection of 1/8 grain (0.0081 Gm.) thirty or forty minutes later. The anesthetic used in all the cases consisted of nitrous oxide and oxygen supplemented occasionally with small amounts of ether. This was administered by an anesthetist of many years' experience. The factor of anesthesia was thus constant in all the studies. In a considerable number of control operations such as excision of tuberculous glands of the neck, herniotomy

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4. Cannon, W. B.: The Emergency Theory of the Adrenal Medulla in Pain and the Major Emotions, *Am. J. Physiol.* **33**:356, 1914.

5. Crile, G. W.: Protection of the Patient in Surgery on the Thyroid., *Surg., Gynec. & Obst.* **32**:213, 1921; The Present Status of Anociation: A Critical Review, *Ann. Surg.* **86**:251, 1927.

and simple appendectomy it was noted that nitrous oxide alone produced little change in the pulse rate, blood pressure or respiration. Patients were protected in every ordinary way, but it was not possible to carry out the minute details of anoci-association observed by Crile. However, we are confining ourselves to interpretation and explanation of the operative reactions themselves, rather than offering means of combating them.

In a small series of recent cases carefully studied, the following routine was adopted: On the morning of operation, observations were made on the pulse rate, blood pressure and temperature. Samples of blood were taken for blood counts and blood sugar determinations. The preliminary injection of morphine had been given, and the same observations were repeated on the arrival of the patient in the operating room and again immediately before the anesthetic was begun. Similarly, observations were made at intervals during the operation and during the immediate postoperative period and, in some instances, at various times during the forty-eight hours or more after operation. The findings following operation are interesting but are not included in this preliminary report.

#### REPORT OF CASES

##### *CASE 1.—Clinical Behavior of a Patient with a Highly Toxic Exophthalmic Goiter Before, During and After Thyroidectomy.*

*History.*—Miss A., representative of the group of young persons suffering with highly toxic hyperthyroidism resulting from exophthalmic goiter, was 24 years of age and had had progressive hyperthyroidism over a period of one year. The thyroid gland was definitely enlarged and showed marked vascularity. Her eyes were strikingly prominent, and there had been a great loss of weight. The pulse rate varied between 120 and 130. After ten days of preparatory treatment with iodine, the pulse rate diminished to 110. The basal metabolic rate before this period was plus 52.9 per cent, and following the ten days of treatment with compound solution of iodine it fell to only plus 45 per cent, and the clinical improvement was not marked. Four days later the patient was operated on. At this time it was not considered safe to do more than a right hemithyroidectomy, which was performed at 10:30 a. m. on April 14, 1933.

*Preoperative Period.*—The patient was reasonably calm while in her room. Unfortunately, there was a delay in the operating room before the anesthetic was administered. The patient became restless; her face was flushed, and, as a result of this period of waiting, there was a definite rise in the pulse rate and also in the rectal temperature. The respirations and the blood sugar were also increased. This is a known response to emotion, particularly fear and apprehension. There was a slight fall in the blood pressure, which might be attributable to the moderate dose of morphine. There was as yet no decided change in the total white blood count or in the differential count. The rectal temperature rose 0.4 F. during this period. At the same time the pulse rate rose from 108 to 135. There was a slight diminution in the total leukocyte count, with a relative rise in the polymorphonuclears and a fall in the mononuclears. The systolic blood pressure fell slightly, but there was a rather definite fall in the diastolic pressure, thus increasing the pulse pressure even before the anesthetic was begun.

*Operative Period.*—Immediately before and more particularly immediately after anesthesia was begun, we found a decided change in all the reactions. The behavior of each reaction up to its maximum, which appears in about from twenty-five to thirty-five minutes after the beginning of the anesthesia and the operation, is given.



**Pulse:** The pulse rate rose from 144 to 180, an increase of 36 points, and during a short period it reached 190, but we did not attribute these 10 points to the operative procedure per se, because there was slight pressure momentarily on the trachea during the delivery of the lobe. Throughout the operation there was no other embarrassing factor of this character, the anesthesia being satisfactory. There occurred an increase in the pulse rate of 72 points from the normal of 108 when the patient was in her room to 180 at the peak of the reaction.

**Blood Pressure:** The systolic blood pressure dropped from the preoperative level of 140 mm. to 124 mm. of mercury and then rose to a peak of 176 mm. Simultaneously, the diastolic pressure was maintained at the low level of about 65. Accordingly, the pulse pressure was increased from the preoperative normal of 50 to 108, an increase of 58 at the height of the reaction.

**Leukocytes:** There was a striking increase of 10,400 in the total white cell count, namely, from 7,250 to 17,650 at the peak of the reaction. The count had thus more than doubled.

**Differential Blood Count:** The polymorphonuclear leukocytes, which showed a slight rise up to the time the anesthesia was begun, immediately and precipitously fell from 63 per cent to 34 per cent just after the peak of the reaction. The mononuclear leukocytes, which showed a preliminary slight fall, rose precipitously during this interval to 66 per cent. Thus, the differential picture before operation was reversed during operation.

**Blood Sugar:** Furthermore, there occurred a moderate rise of the blood sugar from 80 mg. per hundred cubic centimeters of blood, while the patient was in her room, to 95 mg. just prior to administration of the anesthetic. Following this there was a definite increase to 120 mg. just after the peak of the reaction. There was thus an increase of 40 mg. in the blood sugar.

**Rectal Temperature:** During all this time the rectal temperature rose from 98.8 F., when the patient was in her room, to 101.2 F. at the peak of the reaction, namely, an increase of 2.4 F.

After the peak of the reaction had passed there was a gradual tendency to a restoration of the previous preoperative picture, although all the factors did not behave in the same way.

*Period of Subsidence of Reactions.*—The operative reactions after the peak had been reached and during the postoperative period to 5:30 p. m., seven hours after operation, were studied next.

**Pulse:** The pulse rate gradually fell from the peak of 180 during operation to 158 at the end of operation, and to 118 in the evening.

**Blood Pressure.** The systolic blood pressure fell less strikingly, from 176 at the peak to 156 at the end of the operation, and then gradually diminished to 146 in the evening, thus remaining slightly above the preoperative normal pressure, which was 140.

The diastolic pressure rose from its low point of 60 at the peak of the operation to 70 at the end of the operation, and then gradually increased to 90 in the evening. Thus, the pulse pressure, which was much increased from 50 before operation to 108 during the operation, had returned to 50 or to the preoperative normal by evening.

**Leukocytes:** The total white cell count behaved in a strikingly opposite manner; that is, while the remaining operative reactions were tending to return to the preoperative normal the leukocytes continued to increase. Thus the peak of 17,650 was maintained practically to the end of the operation. During the postoperative period there was a further increase to 26,600 as compared with a preoperative

normal of 7,250. This occurred about one and one-half hours after the completion of the operation, and in the evening the white cell count was still high, namely, 19,250. The postoperative rise in the white cell count has been previously observed and reported by Meleney.<sup>6</sup> We believe that this increase in the white cells, largely of polymorphonuclear type, is a reaction to trauma and serum absorption, and not to the suprarenal factor.

**Differential Blood Count:** The mononuclear count following the peak of the reaction fell precipitously from 66 to 33 per cent at the end of the operation, and finally dropped to 13 per cent at 5:30 p. m. Conversely, the polymorphonuclear count rose abruptly from its low point of 34 per cent during the operation to 47 per cent at the end of the operation and to 87 per cent at 5:30 p. m. Thus, in chart 1 there is a crossing of the lines twice as a result of the changes in the differential count, the polymorphonuclears showing a definite decrease in number during the operation and a marked rise much above their normal level at the end of the operation. The reverse holds true with reference to the mononuclears, which show a definite rise during the operation and a precipitous fall to 13 per cent in the evening.

**Blood Sugar:** The blood sugar level was maintained at its high operative level of from 120 to 125 mg. per cubic centimeter of blood during the subsequent two and one-half hours. Further determinations were not made in order to avoid disturbing the patient by puncture of a vein.

**Rectal Temperature:** The temperature gradually fell from its highest point during operation, 101.4 F., to 99.6 F. in the evening.

There was a definite and positive reaction on the part of the patient subjectively and particularly objectively. We have described these operative reactions in detail in order to compare them with the similar reactions observed four days previously in the same patient after the hypodermic administration of 0.5 cc. of 1:1,000 solution of epinephrine. In general, there is a striking parallelism, in the reactions to operation and to epinephrine, as is well illustrated in charts 1 and 2. The differences are those of degree rather than character, the operation in this case causing a more definite response than is brought out by the injection of 0.5 cc. of epinephrine hydrochloride.

**Clinical Response to the Injection of Epinephrine Hydrochloride.**—The response to the injection of 0.5 cc. of 1:1,000 solution of epinephrine (chart 2) given on April 11, three days before this patient was subjected to thyroidectomy, follows. Observations similar to those which were made at the time of operation and which have been described had been previously made in a study of the clinical response of this patient to the hypodermic injection of epinephrine hydrochloride. The patient's normal was established in regard to the various observations which we intended to make. These observations were then further continued after the injection of the epinephrine hydrochloride. The patient was relatively calm and composed during the preinjection period. A summary of the reactions is given here (chart 2).

**Pulse:** The preinjection pulse rate averaged 125. There was an abrupt rise to a peak of 178 in from five to ten minutes, an increase of 53 points. Thereupon the pulse showed a continual gradual fall to the preinjection level of 125; one hour after the injection and continuing for another half hour it fell to 120, or just below the preinjection level.

6. Meleney, F. L.: A Study of Anteoperative and Postoperative Blood Counts in Noninfective Surgical Conditions. *Ann. Surg.* 67:129, 1918.

**Blood Pressure:** The systolic blood pressure taken when the patient was resting quietly in bed was rather constant at 145 mm. of mercury. Immediately after the injection of epinephrine hydrochloride there was a precipitous rise which reached its peak at 198 in a period of eight minutes, an increase of 53 mm. of mercury. There was a fairly prompt fall to 156 in thirty-five minutes, and then a gradual fall to 132 in one and one-half hours following the injection, at which time the reaction had practically subsided. The diastolic pressure beginning at 68 rose sharply to 92 at the peak, at which time the pulse pressure had increased to 106, as compared with the preinjection pressure of 78. A definite

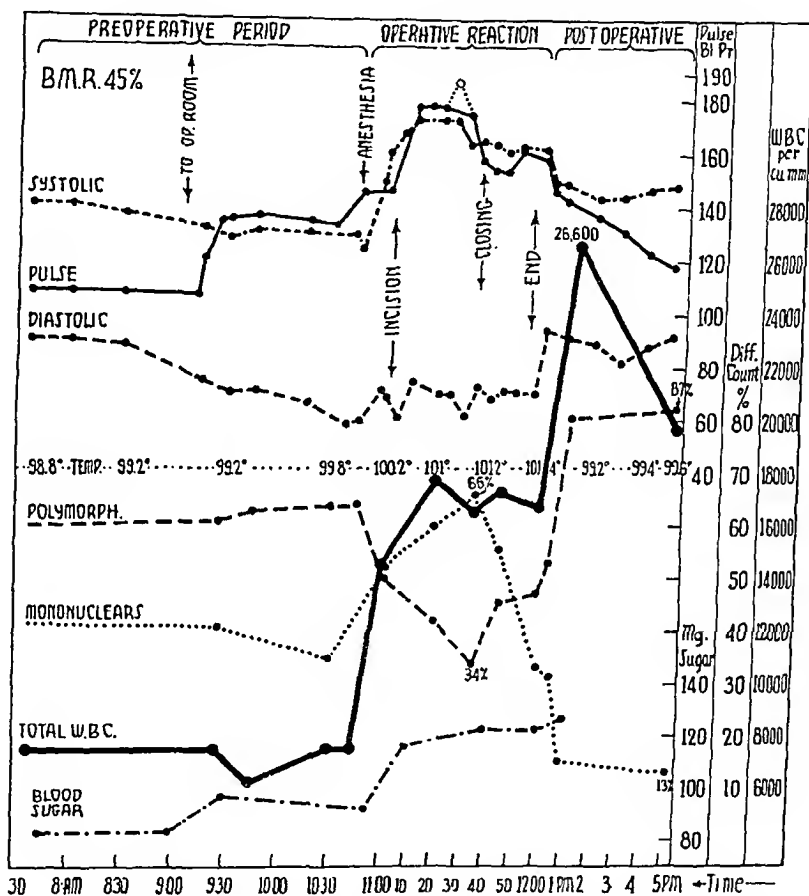


Chart 1 (case 1).—Clinical chart in a case in which right hemithyroidectomy was performed on April 14, 1933. The chart is divided into the preoperative, operative and postoperative periods, and shows graphically the striking changes which occur during these periods in the pulse rate, blood pressure, leukocytes, blood sugar and temperature in response to the operative procedure.

increase of pulse pressure was maintained over a considerable period following the injection of epinephrine hydrochloride and resulted largely from a continued fall of the diastolic pressure.

**Leukocytes:** The total white cell count rose from its preinjection level of 7,550 to 11,650 at its peak, an increase of 4,100 in about twenty minutes after the injection. The count then gradually fell at the end of one and one-half hours to 7,400, which was just below the preinjection level.

**Differential Blood Count:** The differential blood count showed striking changes. The preinjection percentage of the polymorphonuclears was 59; after the injection there was a precipitous fall to 42 per cent in twenty minutes, and then during the remainder of the period there was an abrupt rise after one and one-half hours to 72 per cent, namely 13 per cent above the preinjection level. The reverse was true of the mononuclears, which rose abruptly from a preinjection level of 41 per cent to 58 per cent in twenty minutes and then fell rather abruptly after one and one-half hours to the low of 28 per cent, about 13 per cent below

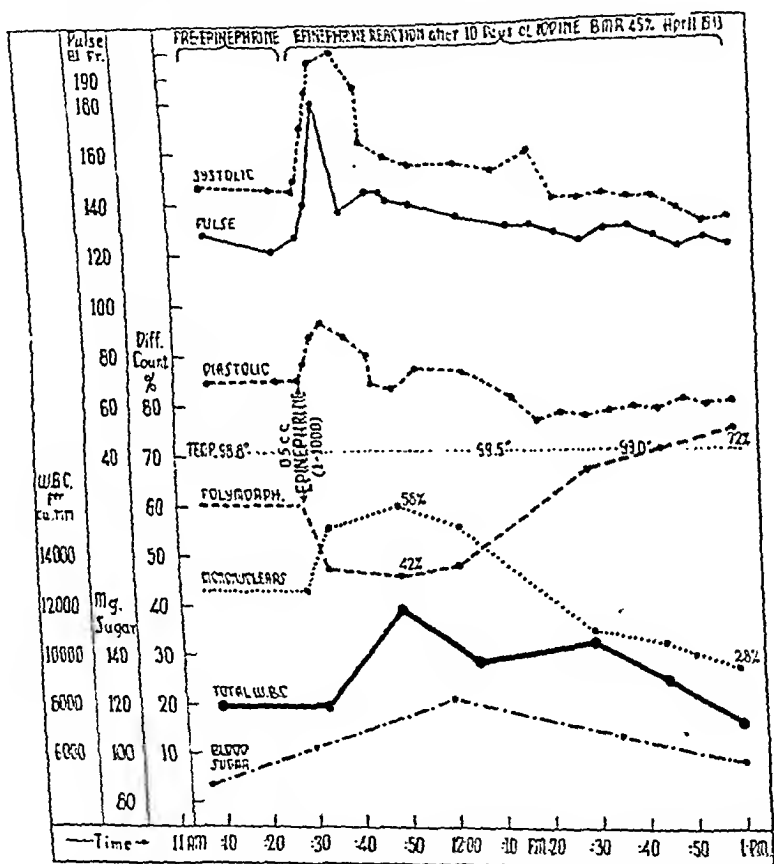


Chart 2 (case 1).—Clinical chart showing the changes which occur in the pulse rate, blood pressure, leukocytes, blood sugar and temperature in response to the subcutaneous injection of 0.5 cc. of 1:1,000 solution of epinephrine. These observations were made on April 11, 1933, three days before the hemithyroidectomy. A comparison of charts 1 and 2 shows a striking similarity in the clinical effects produced by operation and by the injection of epinephrine hydrochloride. The differences are merely of degree of response and not of general character.

the preinjection level. This behavior of the differential count is precisely like that found during operation.

**Blood Sugar:** The blood sugar rose from the preinjection level of 82 mg. per hundred cubic centimeters of blood to 100 mg. just before the injection of epinephrine hydrochloride, a finding which we attributed to emotion. A peak

of 120 mg. was reached about one-half hour after the injection. Following this, there was a gradual fall at the end of one and one-half hours to 95 mg., 13 mg. above the preinjection level.

**Rectal Temperature:** During the period before the injection of epinephrine hydrochloride, the rectal temperature registered 98.8 F.; forty minutes after the injection, the temperature rose to 99.1 F., and thirty minutes later it was still 99 F.

*Comment.*—A woman, aged 24, suffering from a highly toxic exophthalmic goiter, was subjected to a hemithyroidectomy under nitrous oxide-oxygen anesthesia. Characteristic clinical reactions were produced by this procedure, particularly during the operation, but also preoperatively. They included briefly a sharp rise in the pulse rate from 110 to 190, a rise of 36 mm. of mercury in the systolic blood pressure, an increase of 58 points in the pulse pressure, a marked leukocytosis characterized by an increase of 10,400 in the total white cell count and a striking mononucleosis during operation followed by a secondary fall in the percentage of mononuclears toward the end of the operation; synchronously with this there occurred a preliminary fall in the percentage of polymorphonuclears and a secondary rise which continued to increase during the postoperative period, an increase in the blood sugar of 40 mg. per cubic centimeter of blood, and finally an increase of 2.4 F. in the rectal temperature. After the maximum reaction had been reached during operation, there was a tendency to a restoration of these reactions to their preoperative normal, with the exception of the continued changes during the postoperative period in the total white cell count and in the differential picture.

Similar observations were made on the reactions in the same patient during an epinephrine test (table 1) carried out three days before operation. It was found that when a dose of 0.5 cc. of epinephrine hydrochloride was injected hypodermically precisely the same characteristic reactions were produced as when thyroidectomy was performed. The differences are those of degree of reaction and not of general character. It is unnecessary to enumerate in detail the responses to the epinephrine hydrochloride. A striking similarity is noted in the responses to operation and in those produced by the epinephrine in the same patient. This is well illustrated by reference to charts 1 and 2. The injection of a larger dose of epinephrine hydrochloride would doubtless duplicate the somewhat greater degree of reaction produced by operation, but this would not be justified. It might even be unsafe. We have good reason to believe, therefore, that epinephrine plays a large rôle in the production of the operative clinical picture. We have studied a number of cases of exophthalmic goiter of varying degrees of toxicity from the rather mild cases to those of moderate intensity, and briefly, the reactions both to operation and to epinephrine, as would be expected, are of a correspondingly less marked intensity. Similarly.

the reactions in patients with toxic adenoma are definitely less marked than those we have described in the case of exophthalmic goiter.

TABLE 1.—*Clinical Reactions to the Hypodermic Injection of Epinephrine Hydrochloride in Case 1*

Time	Pulse	Respiration	Blood Pressure	Blood Count	Comment
11:00	140	25	150/74	.....	General status, subjective relaxation; objectively patient is somewhat nervous and upset; precordial and neck pulsations are fairly prominent; fairly marked finger tremor; hands warm and mildly moist Blood sugar average before injection of epinephrine, 82 mg. per 100 cc. of blood Temperature, 98.5 F. Status the same
11:10	...	...	...	.....	
11:10	126	27	146/68	W.B.C. 7,500 Pmn. 59% Mono. 41%	
11:24	120	26	145/68	.....	
11:25	...	...	...	.....	Specimen of blood taken (sugar, 160 mg. per 100 cc.)
11:31	...	...	145/76	.....	Injection of epinephrine hydrochloride (0.5 cc. of 1:1,000 solution)
11:32	125	...	168/84	.....	Feels weaker; "catching her breath"
11:34	...	30	186/90	.....	
11:35	178	...	194/90	W.B.C. None Pmn. 46% Mono. 54%	Precordial throbbing; pallor of face; dyspnea; restless
11:39	134	26	159/86	.....	Slow, strong beats alternating with more rapid ones; precordial throbbing; tremor increased; hands dry and warmer; feels better
11:43	144	20	180/78	.....	Beats of equal force now; rate is regular and now stabilized
11:45	144	20	162/68	.....	Rate and depth of respiration increased; pallor disappearing; precordial and neck throbbing still present; not conscious of much disturbance; hand and finger tremor still marked; hands warm and dry
11:50	140	26	158/66	W.B.C. 11,630 Pmn. 42% Mono. 58%	Diminished clotting time, making smear taking difficult; feet feel warm
11:55	128	24	156/74	.....	Hands warm, slightly moist; feet slightly cool to palpation
12:00	...	...	.....	.....	Specimen of blood taken (sugar, 120 mg. per 100 cc.)
12:05	124	25	156/72	W.B.C. 9,630 Pmn. 43% Mono. 57%	Feels more relaxed and comfortable; moderate finger tremor still present
12:10	...	...	...	.....	
12:15	120	27	132/62	.....	Rectal temperature, 99.1 F. Feels quite relaxed, comfortable; somewhat tired; finger tremor still present and moderate in degree; hands warm and dry; cardiac and neck pulsations still increased but moderate
12:20	120	25	155/52	.....	
12:25	128	28	140/56	.....	
12:30	126	25	140/54	W.B.C. 10,500 Pmn. 63% Mono. 37%	Same status
12:35	128	25	142/56	.....	
12:40	128	25	140/58	.....	Specimen of blood taken (sugar, 105 mg. per 100 cc.)
12:45	124	30	140/58	W.B.C. 8,630 Pmn. 69% Mono. 31%	Rectal temperature, 99 F. Status generally the same; is now more comfortable; cardiac and neck pulsations about the same as before injection of epinephrine; hands warm, mildly moist
12:50	120	25	126/60	.....	
12:55	124	25	130/58	.....	
1:00	122	28	132/58	W.B.C. 7,400 Pmn. 72% Mono. 28%	Specimen of blood taken (sugar, 95 mg. per 100 cc.)

CASE 2.—*Clinical Behavior of a Patient with a Mildly Toxic Adenoma (Fetal) During the Preoperative, Operative and Postoperative Phases of Operation for Excision of Adenoma.*

History.—The patient, representative of the group of relatively young women suffering with mildly toxic adenoma of the so-called fetal type, was 29 years

of age. A small lump was noticed on the left side of her neck after the birth of her first child four years previously. Since first noticing the lump, she experienced slight nervousness, fatigue, emotionalism and irritability. Throbbing of the heart and tremor were not noted. There was an adenoma as large as a small lime in the left lobe of the thyroid gland. It was semifluctuant and produced a feeling of choking on pressure. The pulse rate was 100. The blood pressure was 104 systolic and 66 diastolic. The patient had lost 10 pounds (4.5 Kg.) during the previous four or five years, her present weight being 105 pounds (42.6 Kg.). Excision of the adenoma was done on April 5, 1933. The basal metabolic rate after the period of therapy with an iodine preparation was plus 5.9 per cent. There had been no appreciable change in the clinical status following the treatment with iodine.

*Preoperative Period.*—The patient was quiet and composed while in her room at 7:30 a. m. and at 8:00 a. m., at which time she was taken to the operating room. Small doses of morphine had been previously administered. As indicated in chart 3, the changes in the various factors of reaction during this preoperative period were either insignificant or negligible. There was a slight fall in the pulse rate and in the systolic blood pressure. There was no change in the diastolic pressure. There was also a slight diminution in the total white cell count. The differential count showed some changes, such as a slight fall in the percentage of polymorphonuclear leukocytes and a slight rise in the mononuclear cells. There was no change in the rectal temperature. Blood sugar determinations were not made in this case. In other words, the changes noted during the preoperative period were only slight and may be compared with the definite changes noted during the preoperative period in the patient with the toxic exophthalmic goiter previously described.

*Operative Period.*—Pulse: During the period of waiting in the operating room and until anesthesia was started, the rise in the pulse rate was the only really significant change noted. There was an increase from 90 to 120, a rise of 30 points. This compares with a rise of 72 points in the case of exophthalmic goiter under comparable conditions. Subsequently, after anesthesia was begun, the pulse rate rose from 120 to 132. Thereupon there was a temporary fall to 108, with a subsequent rise to 136 and then a gradual decline with oscillations to 120. In other words, there was no further increase in the pulse rate produced by the operation per se than was produced by the preoperative factors concerned. The high point of 132 compares with 190 plus in the case of exophthalmic goiter.

Blood Pressure: The change in the systolic blood pressure was negligible. At the same time there was a preliminary fall in the diastolic pressure of less than 10 points, which was recovered by the time the anesthesia was started. Thus there was no increase of pulse pressure during this preanesthetic interval. After anesthesia was established and the operation begun, the normal systolic pressure of 104 increased just before the middle of the operative procedure to its maximum of 136, following which there was a decline to 128 at the end of the operation—a moderate operative effect. The diastolic pressure, following the establishment of anesthesia and during the operation, tended to fall slightly from 73 to an average of 58, thus increasing the pulse pressure by 30 points, from 40, its normal, to 70, during the maximum effect of the operation. This compares with an increase of pulse pressure of 58 in the case of exophthalmic goiter under comparable conditions.

Leukocytes: There was an insignificant change in the total white cell count, namely, a fall from 5,800 to 5,650. There was a fairly definite increase in the total white cell count during the operation from 5,650 to its maximum of 12,500

at the peak of the reaction, an increase of 6,850 as compared with 10,400 in the case of exophthalmic goiter. At the end of the operation the total white cell count fell to 9,800.

**Differential Blood Count:** During the preoperative period, the percentage of polymorphonuclear leukocytes increased slightly. During the operation there was a relatively moderate fall from 70 per cent to the low point of 62 per cent, a fall of 8 per cent. This was entirely recovered, for at the end of the operation the percentage of polymorphonuclears was 70. These changes differ strikingly from those seen under comparable conditions in the patient with exophthalmic goiter. During the preoperative waiting period there was really no change of significance in the percentage of mononuclear cells, which had fallen from 30 to 25. During the operation there was a slight rise of the mononuclears from 25 to 38 per cent, a rise of 13 per cent; a fall to 30 per cent occurred at the end of the operation, thus making a moderate change in the mononuclear count.

**Blood Sugar Determinations:** The blood sugar was not studied in this case.

**Rectal Temperature:** There was a slight rise of rectal temperature from 98.8 F. before operation to 99.2 F. at the height of operation and 99 F. at the end of the operation. There was an increase of rectal temperature of 0.4 F. as compared with 2.4 F. in the patient with exophthalmic goiter.

**Postoperative Period of Subsidence of Clinical Reactions.**—Following the completion of the operation, there was a fairly prompt recovery, particularly on the part of the pulse rate and blood pressure.

**Pulse:** The pulse rate was rapidly restored to normal within an hour following the close of the operation, following which there was a slight fall, and at the end of the day the pulse rate was 84.

**Blood Pressure:** Similarly, the systolic blood pressure recovered its normal level within an hour, namely, 108, which was maintained to the end of the day. The level of diastolic pressure returned to normal at the end of the operation and remained so to the end of the day.

**Leukocytes:** A progressive increase in the leukocyte count during the post-operative period was found. As previously stated, we feel that this increasing leukocytosis was due largely to the reaction to the wound and was not a response to the operative procedure per se. Thus, a rise in the total white cell count was noted from 9,800 at the end of the operation to 23,900 at the end of the day, seven and one-half hours later. During this same interval the percentage of polymorphonuclear leukocytes had risen from 70 to 96 at the end of the day, and the percentage of mononuclears had fallen from 30 to 4. This reaction is rather strikingly similar to the late leukocytic reaction in the case of exophthalmic goiter, which is another reason for believing that the reaction to the wound and not the suprarenal factor is the cause in both cases, since in other respects there were such remarkable differences.

**Rectal Temperature:** There was no change in the rectal temperature.

In summarizing, there were only moderate subjective and objective clinical reactions in this patient with mildly toxic adenoma during the period of anticipation of the operation, during the immediate preanesthetic period and during the operation. The responses described were all mild or moderate and are to be contrasted with the definitely marked reactions which we found during operation on the patient with exophthalmic goiter. The operative reactions in the patients with exophthalmic goiter and adenomatous goiter are strikingly proportionate to the degree of toxicity indicated clinically and in the metabolic rate. The difference is entirely one of degree, the pattern and tendency of each factor of reaction being the same.



*Clinical Response to the Injection of Epinephrine Hydrochloride.*—The reactions to the subcutaneous injection of 0.5 cc. of 1:1,000 solution of epinephrine given on April 4, 1933, one day before the operation for excision of the adenoma, were the same as those noted during operation and previously described in case 1. Thus, the immediate preinjection status was one of quiet and composure, and there were no changes noted in any of the possible clinical responses.

*Pulse:* The preinjection pulse rate averaged 98. Following the injection of epinephrine hydrochloride, the pulse rate rose promptly and abruptly, but moderately, from 100 to 116; it returned promptly to the preinjection level, and

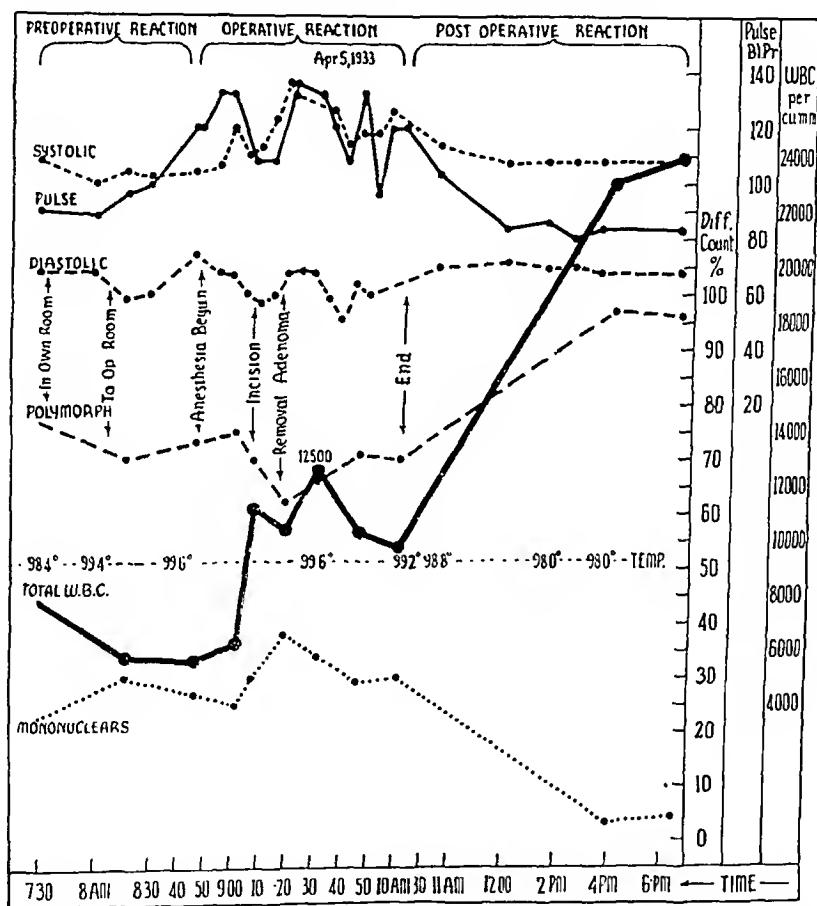


Chart 3 (case 2).—Clinical chart in a case in which a mildly toxic adenoma was excised. The basal metabolic rate after the preparatory treatment with iodine was plus 5.9 per cent. The chart is divided into the preoperative, operative and postoperative periods and shows graphically the relatively mild responses which are produced in the pulse, blood pressure, leukocytes, blood sugar and temperature in consequence of the operative procedure.

then remained at an even level of 104 throughout the period of observation, which was from 11:00 a. m. to 12:30 p. m. There was thus a slight early increase in the pulse rate which soon returned to normal.

*Blood Pressure:* The systolic normal pressure was 110. Following the injection of epinephrine hydrochloride there was a temporary fall to 84 with a sub-

sequent abrupt vertical rise to 126, following which there was a gradual fall to 100 at the end of the period of observation. The diastolic pressure began with a normal of 72, ran parallel with the systolic pressure, fell temporarily to 50 and then promptly returned to 68, thus increasing the normal pulse pressure 18 points, from 40 to 58. Following this the diastolic pressure fell but soon recovered and remained constant at a level averaging 66 to the end of the period of observation. There was thus a moderate increase of 18 in the pulse pressure at the height of the reaction to the epinephrine hydrochloride. This is to be

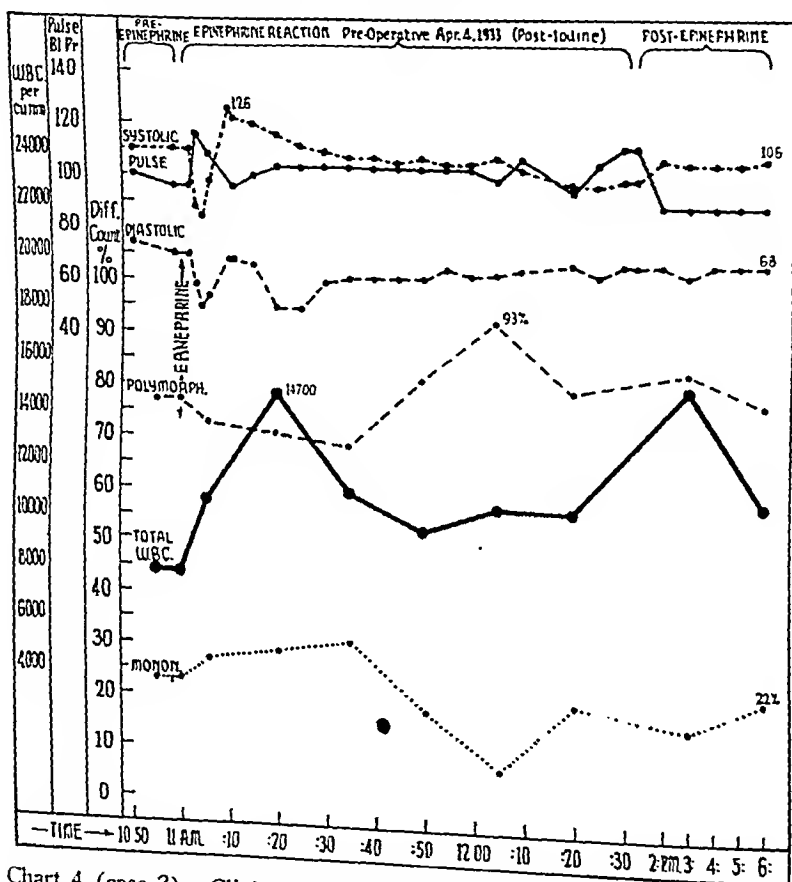


Chart 4 (case 2).—Clinical chart showing the changes which occur in the pulse rate, blood pressure, leukocytes, blood sugar and temperature in response to the subcutaneous injection of 0.5 cc. of 1:1,000 solution of epinephrine. The observations were made on the day before operation. A comparison of charts 3 and 4 shows a marked similarity in the clinical reactions produced by operation and by the epinephrine hydrochloride. The degree of response is approximately the same in each case. Both charts are to be compared with the observations in charts 1 and 2 under comparable conditions in the case of toxic exophthalmic goiter.

compared with an increase of 29 points of pulse pressure under comparable circumstances in the case of exophthalmic goiter.

Leukocytes: The total white cell count rose from the preinjection level of 7,850 to 14,700 twenty minutes after the injection; it fell in the middle of

the test and remained at a constant level, averaging about 10,500. There was a rise in the percentage of polymorphonuclear leukocytes from the preinjection normal of 77 to 93, an increase of 16 per cent at the end of an hour following

TABLE 2.—*Clinical Reactions to the Hypodermic Injection of Epinephrine Hydrochloride in Case 2*

Time	Pulse	Respiration	Blood Pressure	Blood Count	Comment
10:50	100	15	110/74	W.B.C. 7,850 Pmn. 77% Mono. 23%	Calm and relaxed; fine tremor of hands; hands dry; mild pulsations in neck
10:55	96	16	110/70	.....	Status unchanged
11:01	...	..	.....	.....	Injection of epinephrine hydrochloride (0.5 cc. of 1:1,000 solution)
11:02	96	..	110/70	.....	Status unchanged
11:03	116	18	88/58	.....	Increased depth of respiration together with increased rate; deep sigh; feeling of fainting
11:04	...	18	84/50	.....	Circumoral pallor marked; increased neck and cardiac pulsations; slightly increased hand and finger tremor; hands moist; "feet cold"
11:06	108	20	98/54	W.B.C. 10,600 Pmn. 73% Mono. 27%	"Pounding of heart;" increased throbbing of neck; pallor of fingers
11:10	...	..	126/68	.....	Status unchanged
11:11	96	22	122/68	.....	Respiration deeper; cardiac and neck pulsations still marked; hands mildly moist; tremor of fingers still present
11:15	100	20	120/66	.....	Neck and cardiac pulsations moderately marked; "feet feel as though they were getting warmer;" actually cold to the palpating hand
11:20	104	16	116/50	W.B.C. 14,700 Pmn. 71% Mono. 29%	Circumoral pallor less; hands slightly warmer, are mildly moist; finger tremor still present
11:25	104	14	112/50	.....	Status the same; cardiac and neck pulsations still moderately marked; feet still cold; hands still moist; tremor still exaggerated
11:30	104	14	110/60	W.B.C. 11,000 Pmn. 69% Mono. 31%	Feet still cold; status about the same otherwise; cardiac pulsations distinctly less; feels quite relaxed and similar to status prior to injection of epinephrine hydrochloride; finger tremor very mild although definite; hands mildly moist
11:35	104	18	108/62	.....	Status the same
11:40	104	14	108/62	W.B.C. 9,600 Pmn. 62% Mono. 18%	Status the same; blood flows freely from stylet wound in blood puncture
11:45	104	18	106/62	.....	Status essentially the same; hands quite warm, mildly moist; relaxed generally; feet feel warm objectively and subjectively
11:50	104	16	108/62	.....	Patient quite relaxed; hands and feet quite warm; mildly moist; neck and cardiac pulsations now back to normal
11:55	104	16	106/66	.....	Dinner (end of reaction)
12:00	104	16	106/64	W.B.C. 10,560 Pmn. 93% Mono. 7%	
12:05	100	16	108/64	.....	
12:10	108	14	104/66	W.B.C. 10,400 Pmn. 80% Mono. 20%	
12:20	96	24	98/68	.....	
12:25	106	17	96/64	.....	
12:30	112	18	100/68	.....	
12:35	112	18	100/68	.....	
12:45	...	..	.....	.....	
2:00 p.m.	96	16	105/68	W.B.C. 15,100 Pmn. 84% Mono. 16%	
3:00	90	18	106/64	.....	
4:00	90	18	106/68	W.B.C. 10,850 Pmn. 76% Mono. 22%	
5:00	90	18	108/68	.....	
6:00	90	18	108/68	.....	

the injection. Then there was a moderate fall to 82 per cent at the end of the period. The mononuclear leukocytes rose slightly from the preinjection normal of 23 per cent to 29 per cent during the early period of observation, fell to a low of 7 per cent and recovered to 16 per cent at the end of the period of observation.

*Postepinephrine Injection Period.*—All the factors of response were observed from the end of the period of observation at 12:30 p. m. to 6:00 p. m. It is

unnecessary to elaborate in the case of each, and it may be briefly stated that there were no significant changes in any of the factors of response during this period except a temporary increase in the total white cell count at 3:00 p. m. In other words, the reactions had practically subsided in a period of one and one-half hours after the injection of epinephrine hydrochloride.

*Comment.*—The clinical reactions produced by excision of a mildly toxic adenoma in a woman, 29 years of age, tended to be of the same general character, but were relatively far milder (chart 3) as compared with the sharp reactions in the case of the patient with exophthalmic goiter (chart 1). It is unnecessary to enumerate them in detail. On the day before operation, an epinephrine test was done (table 2), and by comparison with chart 4, it is seen that the clinical reactions to the subcutaneous injection of 0.5 cc. of epinephrine hydrochloride were

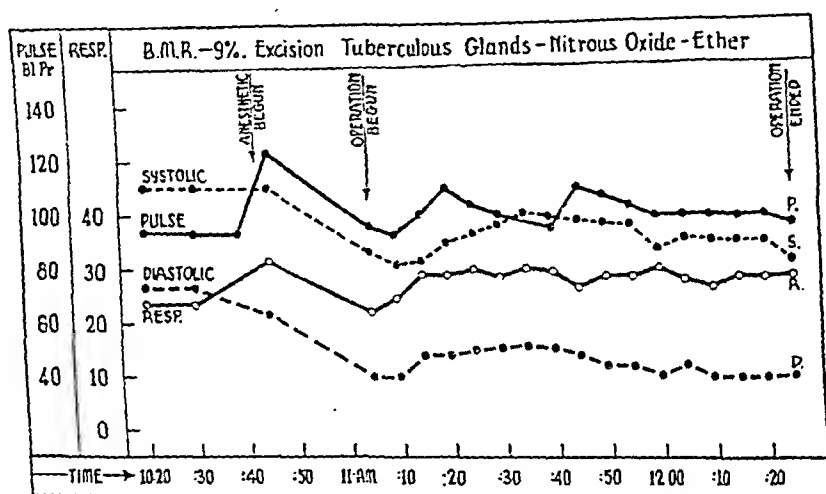


Chart 5 (case 3).—Clinical chart of a control patient showing the absence of clinical reactions on the part of the pulse rate, blood pressure and respirations during excision of tuberculous glands of the neck. The chart shows the absence of clinical response to anesthesia and operation in the patient without hyperthyroidism.

also relatively mild and of the same character as those provoked by operation. Furthermore, it is noted, particularly with reference to charts 1 and 2, that the reactions to operation and to epinephrine were approximately equal and proportional to the degree of toxicity manifested by the patient, clinically and by the metabolic rate. The responses to the injection of epinephrine hydrochloride in the patient with adenoma (chart 4) were far less acute than the reactions in the patient with exophthalmic goiter, observed under similar conditions.

*CASE 3.—Operative Response on the Part of Systolic and Diastolic Blood Pressure, Pulse Rate and Respiration in a Control Case.*

In order to test the factors of anesthesia and operation in other than patients with hyperthyroidism, a number of control subjects were studied with reference

to the reactions of the blood pressure, pulse rate and respiration. The same type of anesthetic was given, and an operation was chosen of a nature somewhat similar to thyroidectomy, namely, excision of tuberculous glands of the neck. The subject chosen for this report was a woman, aged 25, who was in general good health, excepting for the tuberculous glands, and had a basal metabolic rate of minus 9 per cent before operation. There were no significant reactions to the anesthetic or to the operative procedure (chart 4). There was a mild rise in the pulse rate when the anesthetic was started. This returned to normal at the beginning of the operation and remained practically so throughout the operation. There was no rise of the systolic pressure or significant fall of diastolic pressure at the beginning of the anesthesia. In fact, at the time the operation was begun, both fell moderately and then remained at a fairly constant level throughout the operation. Similarly there was no change of significance in the respiratory rate.

#### COMMENT

In a nonsensitive patient, as compared with the sensitive patient with hyperthyroidism, the factors of anesthesia and operation do not have an appreciable effect on the pulse rate, blood pressure and respirations. The etiologic factor which produces such sharp clinical reactions during operation in the sensitive patient with hyperthyroidism is absent in the control patients.

Finally, after observing a large series of control subjects with particular reference to their reactions to operation and to epinephrine, we can state that the responses to both are relatively negative. This holds particularly with reference to blood pressure, pulse rate, respiration and general subjective responses. Our detailed study of control subjects during operation with particular reference to changes in the leukocyte count, blood sugar and temperature is limited. Therefore, general comparisons are not to be made at present. Our purpose is, for the moment, to explain simply the reactions which were found in the active cases of hyperthyroidism. Further studies are being made on normal subjects.

#### SUMMARY

Observations have been made on the clinical reactions exhibited by patients subjected to thyroidectomy. These reactions are seen in a mild degree during the period of anticipation of operation and more intensely during the course of operation.

*Preoperative Period.*—As a result of our studies thus far, we believe that the reactions of the sensitive, toxic patient with hyperthyroidism to operative procedures such as thyroidectomy are definite and readily recognized. The element of emotion, apprehension and fear, with its stimulating effect on suprarenal activity, has been mentioned. The psychic emotional effect of the anesthesia, the element of starvation, operative trauma, possible hemorrhage and other factors produce a definite series of events. These are a preoperative increase of pulse

rate and of systolic blood pressure, and fall of the diastolic pressure. There is also some increase of blood sugar and temperature.

*Operative Period.*—Immediately following the beginning of the anesthesia and during the first twenty-five to thirty-five minutes, the operative reactions reach a maximum characterized by a rather sharp rise of the systolic pressure with a fall of the diastolic pressure. Thus, the blood pressure and hence the load on the heart are definitely increased. Thereafter, there is a gradual subsidence of the systolic pressure and a rise in the diastolic pressure with a restoration at the end of operation of the pulse pressure to the preoperative level. There is a synchronous increase on the part of the pulse, which rises sharply during the early part of the operation and usually falls toward the end. The total white cell count increases soon after the incision is made and continues to rise during the operation and the postoperative period. There is a characteristic behavior of the leukocytes, as shown by the differential count in which, during operation, there is a striking mononucleosis characterized by a sharp increase in the percentage of mononuclear cells. Simultaneously there occurs a marked decrease in the percentage of polymorphonuclear cells. Following the peak of the operative reaction, there is a striking reversal of the picture. The mononuclears fall to a point well below the preoperative level. A continued decline in the mononuclears and an increasing rise in the polymorphonuclears occur during the postoperative period. The blood sugar increases just before and during the operation. We also find an elevation of the rectal temperature which, together with the increase in blood sugar, is sustained and persists for a time during the postoperative period. These reactions briefly described as occurring during operation are reproduced in a remarkably parallel manner before operation by the hypodermic administration of epinephrine hydrochloride. A remarkable similarity is noticed in comparing the behavior of all the reactions manifested during the operation with those that can be produced by the administration of epinephrine hydrochloride. The differences are largely of degree and not of general character. So striking is this parallelism that it has seemed to us warranted to believe that the characteristic clinical reactions which are produced by thyroidectomy for hyperthyroidism are caused by hypersecretion of epinephrine resulting from stimulation of the suprarenal glands. This hyperactivity of the suprarenals is secondary to the disturbing effect of emotion, apprehension, pain, conscious or subconscious manipulation, anesthesia, trauma and all the other factors that comprise a major surgical procedure.

We are not at this time considering the means of obviating these distressing and at times dangerous operative reactions. Crile has pointed the way in the development of his method of anoci-association. Further studies will doubtless lead to the discovery of chemical, physiologic or

surgical means for completely neutralizing or at least greatly minimizing the effect of suprarenal activity during operative procedures. Thyroidectomy in the case of the highly toxic patient suffering with hyperthyroidism would then be less of an ordeal and the postoperative period would be comfortable and even safer than it is at the present time.

### CONCLUSIONS

Critical studies of the clinical responses of patients with hyperthyroidism during the operation of thyroidectomy indicate that a number of characteristic reactions are provoked by such operative procedure.

The operative reactions observed in the patient with hyperthyroidism have been approximately duplicated in character and degree by a small dose of epinephrine hydrochloride subcutaneously administered to the same patient several days before operation.

The similarity of the operative reactions and the responses to the hypodermic injection of epinephrine hydrochloride in the same patient indicate that the former are the result of increased amounts of epinephrine liberated from the suprarenal glands which have been abnormally activated by the various factors comprising the operation.

The manifestations of suprarenal activity which are observed in the clinical reactions before and during thyroidectomy for hyperthyroidism include tremor, throbbing, flushing, perspiration and sharp increases in both the systolic blood pressure and the pulse pressure. There are also a marked increase in pulse rate, an increase in blood sugar and an elevation of body temperature. Furthermore, there are a striking leukocytosis and a marked change in the differential count. There is a definite mononucleosis which begins just before the administration of the anesthetic and continues to increase to a maximum reached in from thirty-five to forty minutes. Synchronous with this absolute and relative increase in the mononuclear cells, there is a sharp fall in the percentage of polymorphonuclear cells. After these maximal changes during operation, the picture is reversed; a sharp fall in the percentage of mononuclear cells occurs with an abrupt rise in the percentage of polymorphonuclear cells to the end of the operation and even beyond. All the operative reactions in the patient with hyperthyroidism were similarly brought out by the administration of epinephrine hydrochloride to the same patient several days previous to operation.

It would appear accordingly that as a result of thyroidectomy for the relief of hyperthyroidism, there is a liberation of an excessive amount of suprarenal secretion. The operative reactions are thus caused by the stimulating effect of this increased amount of epinephrine on the sympathetic nervous system, which has been rendered hypersensitive by the existing hyperthyroidism.

# FIFTY-FOURTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## TUBERCULOSIS

*Human and Bovine Infection; Extrapulmonary Tuberculosis.*—Chang<sup>1</sup> analyzed 200 cases of extrapulmonary tuberculosis to determine the percentage of human and bovine infections. In the whole group, 72.5 per cent were infected with tubercle bacilli of the human type and 27.5 per cent with the bovine type of organism. However, in young children the infection was predominantly bovine (71 per cent in the age group from 1 to 5). This indicates that milk-borne infection still plays a prominent rôle in the younger groups and that pasteurization of milk and tuberculin testing of cattle are still not universal.

*Diagnosis of Surgical Tuberculosis.*—Blair and Hallman<sup>2</sup> advocated attempting to culture the tubercle bacillus as an aid in establishing definite diagnoses. One hundred and fifty specimens of synovial fluid, urine, pus, tissue and pleural exudate were studied. One hundred and six of the specimens were nontuberculous in origin and 44 were tuberculous. The method of culture was that used by Cooper and Uyei. The culture medium was made of crystal violet, glycerin water and

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This report of progress is compiled from a review of 176 articles selected from 293 titles appearing in medical publications approximately between Nov. 4, 1933, and March 1, 1934. Only those which seemed to represent progress were selected for review.

1. Chang, C. S.: New England J. Med. 209:690, 1933.

2. Blair, J. E., and Hallman, F. A.: Diagnosis of Surgical Tuberculosis: Comparison of Diagnosis by Inoculation of Guinea-Pigs and by Culture, Arch. Surg. 27:178 (July) 1933.



potato. Microscopic tests showed tubercle bacilli in smears in from two to four weeks. A culture was usually positive before the time required for the guinea-pig test had elapsed.

*Heliotherapy and Orthopedic Treatment in Surgical Tuberculosis.*—Rollier<sup>3</sup> presented a plea for the treatment of tuberculosis of the joints along conservative lines. He dealt specifically with the disease of the various joints and described briefly the type of treatment employed for each in his clinic. He would rely on the sun and carefully applied physical therapy to develop muscular support to the part, to reform the joint and to restore, at least to some extent, the motion of the joint. He regarded the cold abscess as a "small laboratory where the immunizing bodies were developed." He would aspirate such an abscess only in an attempt to prevent rupture. He would, however, resort to operation to secure good drainage of secondarily infected sinuses with the hope of preventing amyloid disease.

#### PYOGENIC INFECTIONS

*Suppurative Tenosynovitis of the Hand.*—In a report on 200 cases of suppurative tenosynovitis of the hand from Payr's clinic in Leipzig seen between 1919 and 1932, Deicke<sup>4</sup> stated that most of the cases followed insignificant injuries. Cultures were taken only in the more severe cases. Of these, 72 per cent showed streptococci and 28 per cent staphylococci. The thumb and middle finger were affected in 57 per cent of the cases. Increased frequency of the lesions during summer and autumn was observed by the author. The thenar space was involved 19 times and the midpalmar space 35 times. In 61 cases, extension to the forearm occurred. In 1 of these, osteomyelitis of the radius developed. In 52 cases sloughing of the tendon occurred. With the appearance of spindle-shaped swellings of the fingers in neglected cases, involvement of the bone (16 cases) and joint (6 cases) was suspected. In 4 cases, both the bone and the joint were diseased. The wrist was involved 4 times. One patient died, and 2 patients were subjected to amputation. Ankylosis of the wrist occurred in 1 case. The author recommended early small incisions and the induction of Bier's passive hyperemia. Early motion was stressed. The results in terms of function in cases of synovitis were good in 46.5 per cent, fair in 23.9 per cent and bad in 29.6 per cent. In 129, phlegmon results were good in 30.5 per cent, fair in 17 per cent and bad in 35 per cent; the mortality rate was 8 per cent. The age of the patient influenced the results obtained, the poorest results being obtained in the aged.

3. Rollier, A.: Surg., Gynec. & Obst. **37**:220, 1933.

4. Deicke, H.: Beitr. z. klin. Chir. **158**:461, 1933.

*Nontuberculous Abscess of the Psoas Muscle in Childhood.*—Five cases of presumable primary infections of the psoas muscle were described by Klages.<sup>5</sup> A limp, pain in the leg, inguinal adenopathy, increased lumbar lordosis and fever all pointed to the site of the lesion. The outlines of the psoas muscle might be changed in the roentgenogram. Following aspiration of pus, drainage by the extraperitoneal route was advised.

#### ARTHRITIS

*Rheumatism; Clinical Experimental Investigation.*—Copeman<sup>6</sup> considered the facts that the National Health Insurance had to pay nearly 20,000,000 pounds per annum to sufferers from industrial rheumatism and that 6,000,000 weeks of work were lost annually on account of the same condition were ample justification for a strenuous national campaign against the "captain of crippledom." He outlined a comprehensive scheme, and, in vindication of an active instead of a "defeatist's" attitude toward the diseases, cited the figures of the Petro Place Clinic for Rheumatism, which showed 18.6 per cent cures and 54.8 per cent improvements after treatment.

*Development of Neuro-Arthropathies.*—Alajouanine and Mauric<sup>7</sup> called attention to the fact that close observation, clinical and roentgenologic, of patients with neurologic diseases (particularly tabes and syringomyelia) revealed not only little known aspects of the arthropathies but also a recognizable prearthropathic state. The latter consisted of localized bony overgrowth simulating hypertrophic arthritis or a definite atrophy of the substance of the bones. The tarsal joints, fingers and great toes were the most common sites for these seldom recognized arthropathies. Clinically, they were accompanied by what the authors called a pseudo-infectious condition. The tissues were swollen, hot and cyanotic, with dilated veins suggesting a deep sepsis. No treatment was suggested, except that 1 case was reported in which arthropathy of the midtarsal joints was remarkably improved by periarterial sympathectomy.

*Sacro-Iliac Arthritis.*—Willis<sup>8</sup> studied a large number (1,559) of human skeletons, 96 of which showed bony ankylosis in one or both sacro-iliac joints. He felt that these were brought about by one of two ways: by smooth calcification of the anterior common ligament or by irregular lipping of the periphery of the joint. Of specimens of the first type, there were 19, with an average age of 45.9 years; of the latter, there were 6, with an average age of 67 years. In 67 specimens, the

<sup>5</sup> Klages, F.: Beitr. z. klin. Chir. 158:171, 1933.

<sup>6</sup> Copeman, W. S. C.: J. State Med. 41:476, 1933.

<sup>7</sup> Alajouanine, T., and Mauric, G.: Presse méd. 41:1537, 1933.

<sup>8</sup> Willis, T. A.: Surg., Gynec. & Obst. 57:147, 1933.

average age of which was 57.3 years, there was a combination of the two types. Four pelves showed congenital obliteration of the joint. "The bone and joint changes were in direct ratio to the mechanical stress of the upright position." In persons more than 40 years of age, lippling of the axial skeleton and acetabulum was practically universal, and increased with age.

#### NEOPLASMS

*Radiosensitivity of Tumors.*—Space does not permit complete reprinting of this editorial<sup>9</sup> as a whole. It presented an excellent summary of the present knowledge on the radiosensitivity of tumors, however, and should be read in its entirety. Some points that were brought out were: 1. Radiosensitivity of tumors is no accidental attribute but an expression of all structures as well as parent tissue. 2. Location of a tumor, particularly in bone or fat, renders it radioresistant. 3. Tumors develop resistance to both roentgen rays and radium. 4. The degree of malignancy has little to do with radiosensitivity. Differences in reaction become clear when it is remembered that there are similar differences in normal cells. Sensitivity seems related to the natural life cycle of the cell. Finally, the standardization of dosage and the artificial increase in radiosensitivity are reviewed.

*Results of Irradiation in Treatment of Operable Osteogenic Sarcoma of Long Bones.*—The controversy over the method of treatment of osteogenic sarcoma without demonstrable metastasis has long raged. Coley,<sup>10</sup> after a review of his own cases as well as those in the Registry of Bone Tumors, concluded that there was a growing number and an increasing percentage of five year cures in spite of pessimistic reports to the contrary. He reported 33 five year cures. The treatment of choice was amputation without biopsy or preoperative irradiation. Post-operative irradiation also probably was useless, but the use of erysipelas and prodigious toxins (Coley's) postoperatively was beneficial. Endothelial myeloma (Ewing's tumor) responded best to irradiation and the toxins used simultaneously.

#### SPINE

Ghormley<sup>11</sup> stated that many cases of pain low in the back were due to pathologic changes in the articular facets. These changes could often be shown roentgenographically by oblique lateral views of the spine. Treatment of pain of this type should be essentially conservative, but nevertheless there were certain indications for operation. Ghormley

9. Radiosensitivity of Tumors, editorial, J. A. M. A. **102**:619 (Feb. 24) 1934.

10. Coley, W. B.: Radiology **21**:318, 1933.

11. Ghormley, R. K.: Low Back Pain, with Special Reference to Articular Facets, with Presentation of Operative Procedures, J. A. M. A. **101**:1773 (Dec. 2) 1933.

enumerated the conditions, some or all of which should be satisfied before operation was recommended: (1) persistent or recurrent attacks of pain over a period of months, (2) pain localized to a definite area, (3) narrowing of the intervertebral disk, (4) changes in the intervertebral articulations and (5) examination of the central nervous system with negative results. It was not possible to select those patients whose trouble lay solely in the facet; therefore a lumbosacral fusion or excision of the lumbosacral articular facets was performed.

*Enlargement of Intervertebral Disk Associated with Decalcification of the Vertebral Body.*—Moffat<sup>12</sup> suggested that the enlargement of the vertebral disk seen frequently with pathologic fractures was due to simple hypertrophy of the disk and not to rupture of the nucleus. Five cases were reported to substantiate his claim.

#### SCOLIOSIS

*Removal of Vertebral Bodies in the Treatment of Scoliosis.*—Von Lackum and Smith<sup>13</sup> removed a vertebral body in each of 10 cases to correct scoliosis. In 5, the scoliosis was caused by a hemivertebra; in 5 others, the cause of the scoliosis was unknown. They found that removal of a dorsal vertebra was not practical because of hemorrhage and shock. The lumbar vertebrae were removed in two stages, the technic of which was described. The age of the patients varied from 1½ to 22 years, the average being 11½ years. The authors felt, however, that the operation should not be done on a person less than 6 years of age. Removal of the vertebra was in each case followed by spinal fusion and correction of the curve by means of plaster of paris jackets.

#### CIRCULATORY DISTURBANCES OF THE EXTREMITY

*Thrombo-Angiitis Obliterans.*—Samuels<sup>14</sup> discussed the general treatment of this disease based on experience with about 300 cases. Twelve cases were reported in detail. He stated that except in rare instances (less than 1 per cent) amputation was not indicated. Treatment consisted of: (1) rest in bed with the limb constantly horizontal, (2) prohibition of tobacco, (3) intravenous injections of hypertonic saline solution (from 2 to 5 per cent) in doses of 300 cc. every other day, depending on the severity of the case, and (4) surgical cleanliness of the affected areas with the application of anesthetic oint-

12. Moffat, B. W.: *J. Bone & Joint Surg.* **15**:705, 1933.

13. von Lackum, H. L., and Smith, A. De F.: *Surg., Gynec. & Obst.* **57**:250, 1933.

14. Samuels, S. S.: *Gangrene Due to Thrombo-Angiitis Obliterans: Further Experiences with Treatment.* *J. A. M. A.* **102**:436 (Feb. 10) 1934.

ments in the painful stage. Samuels believed that sympathectomy and ganglionectomy had no place in the treatment of this condition.

[ED. NOTE.—There is much still to be learned concerning the peripheral circulatory disorders. This report, if confirmed by others, would suggest that less radical therapy was indicated.]

*Topical Diagnosis of Embolism of the Extremities.*—Paresthesia, pain, coldness, pallor and anesthesia for small movements and muscular palsies were the usual signs, according to Dick,<sup>15</sup> of local ischemia, but these signs did not permit the localization of an embolus in the extremity because of the development of collateral circulation. Occasionally local pain might be felt on the lodgment of an embolus. Rarely was the embolus palpable, even in emaciated persons. Local tenderness at the site of lodgment of the embolus as well as absence of pulsation was sometimes of help. Arteriography was of value in localizing the embolus in 1 case. The poor results in attempted embolectomy were usually referable to: (1) repeated showers of emboli occurring in severe cardiac or vascular disease, (2) an embolus that was allowed to remain in place so long that thrombi extended from it into the smaller vessels owing to injury of the vascular intima and (3) often difficult localization of the point of vascular occlusion.

#### INTERNAL DERANGEMENT OF THE KNEE JOINT

*Osteochondritis Dissecans.*—After describing some cases of osteochondritis dissecans, especially those in which the knee joint was affected, Fairbank<sup>16</sup> discussed the various theories of causation which have been advanced to explain this condition. He came to the conclusion that trauma alone could explain all cases satisfactorily. The mechanism of the trauma, in the case of the knee joint, was taken to be a violent rotation inward of the tibia which drove the tibial spine against the inner condyle of the femur.

[ED. NOTE.—The editors believe that the etiology of osteochondritis dissecans is more complex than this article would lead one to believe. There is equally good evidence for an embolic theory of causation.]

*Diagnosis and Results of Injuries of the Meniscus.*—In 134 arthrotomies performed at Schloffer's clinic at Praha, Spira<sup>17</sup> found 84 injuries of the menisci. Most of the cases were traumatic in origin. The meniscal lesions observed at operation were: tear of the anterior horn, 11 times; tear of the posterior horn, 9 times; longitudinal tear, 6 times; "bucket handle" tear, 14 times; transverse tear, 15 times;

15. Dick, W.: Beitr. z. klin. Chir. **158**:481, 1933.

16. Fairbank, H. A. T.: Brit. J. Surg. **21**:67, 1933.

17. Spira, E.: Beitr. z. klin. Chir. **158**:1517, 1933.

displacement of the anterior horn, 14 times, and indefinite displacement, 4 times. In the patients reexamined (postoperative period not given), an excellent result was observed in 72.1 per cent, a good result in 22.4 per cent and a poor result in 6.6 per cent.

#### THE FOOT

*Manipulative Treatment of Painful Feet.*—That manipulative treatment, followed by exercises to maintain and improve the flexibility and strength of the feet, brought about a cure in 83 per cent of cases of "chronic foot strain" was stated by Wiles.<sup>18</sup> The joints most commonly affected in the first instance were the midtarsal joints, but in late cases it was sometimes impossible to find the primary site of strain and formation of adhesions. Certain cases of chronic arthritis were suitable for manipulative treatment, but considerable care had to be exercised in selection. The manipulative technic advocated was described.

[ED. NOTE.—Forceful manipulations for disabilities of the foot, an extremely popular procedure by certain cultists and physicians, is fraught with considerable danger unless careful selection of cases is made. The cases which respond most favorably to this procedure are rigid flatfoot without too great bony distortion and early arthritic deformities when extensive ankylosis has not occurred. Manipulation must be followed in every case by apparatus to maintain temporarily the corrected position and by prolonged exercise to regain strength. In the feet in which marked bony deformation has occurred, plastic operations on the bone should be the therapy of choice.]

#### MISCELLANEOUS

*Arthropneumoroentgenography.*—In a well illustrated article, Oberholzer<sup>19</sup> described his experience with visualization of joints. In his hands diagnosis of most internal derangements could often be made accurately by this method.

*Serum Treatment of Gas Edema.*—Löhr<sup>20</sup> believed that there was evidence of definite clinical value of the German serums used in the prevention and treatment of gas gangrene. He felt that a multivalent serum should be used since of the many strains of *Bacillus welchii* known all were pathogenic. The immediate intramuscular injection of serum in large amounts was advocated since the spread of the infection was a matter of hours.

18. Wiles, P.: Brit. M. J. 2:563, 1933.

19. Oberholzer, J.: Beitr. z. klin. Chir. 158:113, 1933.

20. Löhr, W.: Beitr. z. klin. Chir. 158:571, 1933.

*Rupture of the Quadriceps Tendon.*—Lenormant and Olivier<sup>21</sup> found rupture of the quadriceps tendon to be comparatively rare. The mechanism of such injury was a severe muscular effort to regain the upright position when the knee was suddenly flexed. The patient might fall onto the knees, but the rupture was due to the pull of the muscle and not to a direct blow. Certain predisposing causes were found which accounted for the frequency with which the lesion was bilateral. Rupture occurred in patients over 40 years old. Diabetes, chronic arthritis and arteriosclerosis were possible factors. It was seen associated with calcified deposits in the quadriceps tendon. Treatment consisted of operative repair with catgut or fascia and early mobilization. Age was no contraindication to operation as repair could be done under local anesthesia. The results were uniformly good. An interesting comparison was made with the results in a series of 85 cases in which no operative treatment was used. These results were: good, 34; poor, 35, and bad, 16.

#### ORTHOPEDIC OPERATIONS

*Hip Fusion Operation.*—Chandler<sup>22</sup> described an operation using a massive graft from the trochanter and upper end of the femur, similar to that of Hibbs. The approach was by a long vertical-lateral incision through the gluteus medius, tensor fascia lata and vastus lateralis. Heavy osteoperiosteal flaps of cancellous and cortical bone were reflected from the anterolateral and posterolateral aspects of the trochanter. A long massive graft, including the great trochanter, the distal lateral aspect of the neck and the upper end of the femur, was cut out and turned end for end. The upper end of the graft was inserted into a recess in the ilium made by elevating a flap of the outer table. The distal end of the graft lay in the groove from which it was removed and was covered by the osteoperiosteal flaps which fell back over it.

*Extra-Articular Bone Graft Treatment for Tuberculosis of the Hip Joint with Especial Study of Primary Failures of Fusion.*—Haas<sup>23</sup> studied the results in 50 cases of extra-articular fusion of the hip for tuberculosis in children. The average age was 7 years. Six patients presented sinuses at the time of operation, but only 1 failed to heal during convalescence. The average duration of the disease was 4.3 years. Forty per cent, or 20 patients, required more than one operation. Conditions which favored fusion were: (1) chronicity and quiescence of the disease, (2) approximation of the trochanter to the acetabulum, (3) little motion in the hip and (4) absence of abscess or sinus at the time of operation, although the presence of these did

21. Lenormant, C., and Olivier, C.: *Presse méd.* **41**:1561, 1933.

22. Chandler, F. A.: *J. Bone & Joint Surg.* **15**:947, 1933.

23. Haas, S. L.: *J. Bone & Joint Surg.* **15**:743, 1933.

not necessarily mean disaster. The routine operation was to turn flaps of bone down from the ilium to between the trochanter and femur, unless failure of fusion was anticipated, in which event an osteoperiosteal graft was also taken from the tibia.

*Extra-Articular Arthrodesis of the Shoulder.*—Watson<sup>24</sup> concluded that a solidly arthrodesed joint was the best end-result to be obtained in tuberculosis of the shoulder joint. He believed that the extra-articular method was best in these cases and devised a new operation which had yielded excellent results in the 3 cases he reported. Through a straight incision over the joint of the shoulder the deltoid muscle was removed subperiosteally from its entire origin and turned downward. The cortical layer of bone was removed from the whole acromion process. Without opening the capsule, a bone flap including the greater tuberosity was levered out without breaking it from the humerus. Partial osteotomy of the clavicle was then performed under its outer end, and the spine of the scapula was also partially fractured at a similar level. This allowed the acromion to be depressed far enough so that it was securely wedged beneath the flap of bone raised from the humerus on abduction. The wound was closed in layers and the arm immobilized in a plaster spica.

*A New Method of Arthrodesis of the Shoulder Joint.*—Brett<sup>25</sup> pointed out that though bony union resulted, in many cases the result in fusion of the shoulder joint was unsatisfactory because of loss of the angle of abduction during the period of immobilization. He attributed this to faulty scapular fixation. He advocated, in addition to the usual arthrodesis (removal of cartilage from the glenoid and head of the humerus), apposition of the acromion to the great tuberosity and fixation of the humerus and scapula by a dowel graft driven through the head of the humerus and into the glenoid and the body of the scapula. He relied on this graft to maintain the desired abduction until union was solid. Excellent results were obtained in 2 cases.

*Spinal Fusion by Simplified Technic.*—Henry and Geist<sup>26</sup> advocated spinal fusion by "feathering" the laminae with a sharp hand chisel and gouge, thus avoiding the use of a mallet. In addition, the spinous processes were broken down, and a mass of small bone chips removed from the tibia was placed over the bony bed. Good results were obtained in 75 cases by this method.

[ED. NOTE.—This method was similar to that used at the Massachusetts General Hospital for a number of years, except that at that hospital an osteoperiosteal graft was preferred to bone chips, and the

24. Watson, J. R.: J. Bone & Joint Surg. 15:862, 1933.

25. Brett, A. L.: J. Bone & Joint Surg. 15:969, 1933.

26. Henry, M. O., and Geist, E. S.: J. Bone & Joint Surg. 15:622, 1933.



mallet was used over the spine. One of the editors has avoided if possible the use of the mallet on the spine in children, thus diminishing shock.]

*Operative Treatment of Sacro-Iliac Disease.*—Harris<sup>27</sup> reported the results of sacro-iliac arthrodesis in 67 cases. The diagnosis of sacro-iliac disease was made in 296 cases, i. e., 67.5 per cent of all cases examined in which there was pain in the lower portion of the back. Operation was advised but refused in 45 cases, and was not advised in 201 of the 296 cases. The average age in the cases in which operation was performed was about 33 years. The average time of palliative treatment before operation was done was 4.6 months. The Smith-Petersen technic was used. The value of the roentgenographic diagnosis in sacro-iliac strain, except to rule out disease, was questioned. The results in the 67 cases were as follows: freedom from symptoms, 46, or 68.6 per cent; partial relief, 12, or 17.9 per cent; no relief, 2, or 3 per cent; unable to trace, 6, or 8.9 per cent, and dead, 1, or 1.5 per cent. Fusion was done in 3 cases a second time because of persistent symptoms. At operation the grafts were found solid, and though the patients got well, no cause was found for the persistent symptoms. Harris advocated fusion by the Smith-Petersen technic for tuberculosis of the sacro-iliac joint, as well as for cases of persistent strain.

*Amputation Through the Lower Third of the Leg for Diabetic and Arteriosclerotic Gangrene.*—Smith<sup>28</sup> described the technic for amputation in the lower part of the leg for arteriosclerotic and diabetic gangrene and reported illustrative cases. The stumps were drained, the drain being removed without taking down the entire dressing. Too frequent dressings were discouraged. He preferred to avoid the guillotine amputation since the stumps following this procedure were often slow in healing, frequently developed osteomyelitis in the end of the bone and at times were painful. The author would also avoid the Gritti-Stokes operation, trying as often as possible to preserve the knee joint.

*Recurrent Dislocation of the Patella.*—Cole and Williamson<sup>29</sup> listed the predisposing factors in recurrent dislocations of the patella as follows: (1) genu valgum, (2) underdevelopment of the lateral femoral condyle, (3) relaxation of the medial capsule and other patellar attachments and (4) abnormal lateral displacement of the tibial tubercle. Operative procedures were divided into three groups: (1) those directed toward tightening and reenforcing the relaxed structures on the medial

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27. Harris, C. T.: *J. Bone & Joint Surg.* **15**:651, 1933.

28. Smith, B. C.: *Amputation of Leg Through Lower Third of Leg for Diabetic and Arteriosclerotic Gangrene*, *Arch. Surg.* **27**:267 (Aug.) 1933.

29. Cole, W. H., and Williamson, G. A.: *Chronic Recurrent Dislocation of the Patella*, *J. A. M. A.* **102**:357 (Feb. 3) 1934.

side of the patella, (2) those attempting to straighten the line of pull and (3) those that raised the lateral femoral condyle. The methods used were fascial transplants in the first group, transplantation of the tibial tubercle in the second group and raising the anterior surface of the lateral condyle in the third group.

## FRACTURES

*The Abduction Method, Considered as the Exponent of a Treatment for All Forms of Fracture at the Hip in Accord with Surgical Principles.*—Whitman<sup>30</sup> discussed the methods of treating fractures of the neck of the femur, including the abduction (Whitman) method, the methods of traction and those of internal fixation. He stated that for the average patient and for the average fracture of this type "there can be no alternative for the abduction method," and that according to statistics union of the medial fracture was obtained in about 65 per cent of cases in which this method of treatment was used. The failures in 35 per cent were due either to defective treatment or to incapacity for repair. The former should be treated by open operation, and the latter by the reconstruction procedure.

*Treatment for Fractures of the Neck of the Femur.*—Leadbetter<sup>31</sup> advocated for fractures of the neck of the femur manual closed reduction with the patient under a general anesthesia and fixation in plaster for from ten to twelve weeks. The manipulation described by the author consisted in flexion of the thigh and knee to a right angle with traction on the femur in its long axis with the thigh slightly abducted. The leg was then internally rotated 45 degrees and then slowly circumducted into extension, abduction and internal rotation maintaining the traction during the maneuver. He felt that extreme abduction and internal rotation as recommended by Whitman gave less satisfactory apposition of the fragments than a position of slight internal rotation and abduction. If reduction was satisfactory, the leg would maintain internal rotation when supported at the heel alone. He applied a plaster spica with little padding at the pelvis and none on the leg. He stressed the general care of the patient. In 31 cases, 22 patients (70.9 per cent) obtained bony union and 9 (29 per cent) obtained fibrous union. There were 4 deaths (12.8 per cent).

[ED. NOTE.—The attack on this difficult problem is unremitting. Accurate reduction and complete fixation of the fracture, with careful attention to the patient's general health, are the important factors. The manipulation advocated by this author is based on sound mechanical principles.]

30. Whitman, R.: Am. J. Surg. 21:335, 1933.

31. Leadbetter, G. W.: J. Bone & Joint Surg. 15:931, 1933.

*Delayed Appearance of Deformity in the Vertebral Body Fractures.*—Feaster<sup>32</sup> discussed fractures of the vertebral bodies which were not visible in the roentgenogram at the time of injury but which became so after an undetermined interval of a few weeks. He believed the trauma, although not disturbing the homogeneity of the bone, was sufficient to disturb nutrition and to weaken the bone, and later to allow more or less collapse or "wedging." This sequence of events was common enough to make roentgenologic reexamination of the spine after an interval of from two to three weeks a routine measure in all cases in which discomfort persisted. This type of case could result from slight trauma and probably constituted so-called "Kümmell's disease."

*Fractures of the Spine.*—Watkins,<sup>33</sup> in the treatment of spinal fractures, advocated the more "physiologic" treatment which briefly consisted of immediate manual reduction followed by the application of a plaster jacket in hyperextension. The jacket was split and physical therapy started in six days. Active exercise of the erector spinae muscles was considered most important during convalescence. In eight weeks the patient was allowed up wearing a brace, and exercises were continued. It was felt that within six months normal activities could be resumed. The author did not favor operative fusion for treatment of such fractures; nor did Atsatt and Wilson who discussed the paper, and who also advocated correction of the general body mechanics with a view to eliminating permanently the element of strain as a result of the injury.

*Isolated Fractures of Articular Processes of Lumbar Vertebrae.*—Mitchell<sup>34</sup> reported 5 cases of fracture of the articular processes in the spine. All were produced by a direct blow on one side of the spine. Very clear, localized roentgenograms were necessary to demonstrate the fractures. The author felt that if symptoms persisted at the end of three or four months and if there was no roentgen evidence of union, spinal fusion and removal of the loose fragments should be done. He also felt that this injury occurred much more frequently than was evident by the routine roentgenograms of the spine and that such injury might account for many persistent backaches after injuries which were attributed to adhesions, faulty posture or even neuroses.

*Application of Steel Splints to Bone.*—An article by Reinhold<sup>35</sup> cannot be abstracted without the reproduction of diagrams and photographs. It is important, however, because it may offer a solution to the

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32. Feaster, O. O.: Delayed Deformity in Vertebral Body Fractures, J. A. M. A. **102**:598 (Feb. 24) 1934.

33. Watkins, J. T.: California & West. Med. **39**:246, 1933.

34. Mitchell, C. L.: J. Bone & Joint Surg. **15**:608, 1933.

35. Reinhold, P.: J. de Chir. **42**:374, 1933.

too frequent breaking of bone plates and screws, disasters which have continued in spite of the efforts of the American College of Surgeons to standardize bone plates and screws. The fault is probably due to abnormal stress brought about by the fact that drill holes and screws are not properly centered through the holes in the bone plates. The author advised an ingenious guide which is screwed onto the bone plate. Through this guide the dull holes are bored and the screws inserted. The apparatus is simple and not cumbersome. Special screws and plates are necessary, but they are of such type that they can easily be standardized.

#### PATHOLOGY

*Clinical Significance of Structural Transformation Zones in Bones.*—Transformation zones described by Loose in pathologic bone as in rickets and osteomalacia had been found by Walter<sup>36</sup> in normal bone which had been exposed to repeated mechanical trauma. Particularly marked changes occurred if the stresses were bending stresses. The author suggested that the so-called sympathetic lesions of the bone were probably to be explained on the basis of mechanical stress. In his opinion, the so-called aseptic necroses also fell into this group.

*Tissue in Gas Gangrene.*—Suder-Plassman<sup>37</sup> studied the muscular lesions in a fatal case of gas gangrene. He described and showed very well in photomicrographs the edema of the perimysium and the nuclear changes with chain formation, chromatolysis and pyknosis. There was edema of the perineurium with retention of the axis-cylinders and early involvement of the motor end-plates. The capillaries showed a peculiar corkscrew-like angulation. Eventually disintegration of the muscle fibers was observed with formation of "Bowman's disks."

#### RESEARCH

*Healing of Fractures and Bone Defects After Venous Stasis.*—Experiments were performed on 24 dogs by Key and Walton<sup>38</sup> to determine whether venous stasis helped or hindered bony union. The ulna was chosen rather than the fibula, as the latter was small and covered with muscle attachments and therefore unsuitable. In 12 dogs the ulnae were divided with an osteotome, and the veins draining that area were ligated on one side. The veins were ligated immediately in 6 dogs and after a week's interval in the other 6 dogs. In 12 dogs 0.5 cm. of the ulna was resected, and the veins were ligated similarly to those in the first group. Ligation caused marked congestion and

36. Walter, H.: Arch. f. klin. Chir. 178:116, 1933.

37. Suder-Plassman, P.: Beitr. z. klin. Chir. 158:603, 1933.

38. Key, J. A., and Walton, F.: Healing of Fractures and Bone Defects After Venous Stasis. Arch. Surg. 27:935 (Nov.) 1933.

swelling lasting for two weeks. Their results were in marked disagreement with Pearce and Morton.<sup>39</sup> The gross specimens, microscopic slides and roentgenograms showed no difference in healing between the ligated and the unligated sides.

*Studies of Immobilization of Normal Joints.*—In an effort to study the effect of immobilization on joint cartilage, Ely and Mensor<sup>40</sup> fixed the ankle joints of 4 dogs in plaster of paris for periods varying from one to three months. Definite degenerative changes were observed both macroscopically and microscopically, the greatest changes occurring where cartilaginous surfaces were in closest apposition. The changes noted were: (1) close approximation of the articular surfaces, (2) thinning, irregularity, fibrillation and vacuolation, (3) replacement fibrosis and (4) encroachment of areolar tissues on the articular cartilage.

*Osteochondritis of the Head of the Femur.*—Miltner and Hu<sup>41</sup> reviewed the various theories as to the etiology of osteochondritis deformans juvenilis of the head of the femur (Legg-Calvé-Perthes' disease). Of the suggested causes (infection, trauma, embolism and maldevelopment), they considered that deficiency of blood supply to the head of the femur seemed the most likely. They then attempted to produce similar pathologic changes in the femoral heads of young rabbits and dogs. Interruption of the blood supply through the capsule and periosteum of the neck of the femur caused no marked changes, but when in addition to this the ligamentum teres was ligated pathologic changes developed in the head of the femur similar to those described in human osteochondritis juvenilis.

[ED. NOTE.—Again the importance of vascular changes in the production of pathologic changes in the joint is demonstrated in animals. The missing link is the proof that such vascular changes occur, and the explanation of the mechanism of their production in the typical, clinical case.]

*Experimental Investigations as to the Immunobiology of Bone Marrow.*—While trying to produce organotropic strains of streptococci and staphylococci in the fashion of Rosenow, Erb<sup>42</sup> observed that the cultures of these organisms on fresh bone marrow died after a few weeks. Even the use of boiled bone led to similar results, although not quite as striking. He therefore investigated the bactericidal properties further. Animals given injections of staphylococci grown on bone marrow lived longer than those given injections of organisms grown on

39. Pearce, H. E., and Morton, J. J.: *J. Bone & Joint Surg.* **13**:68, 1931.

40. Ely, L. W., and Mensor, M. C.: *Surg., Gynec. & Obst.* **57**:212, 1933.

41. Miltner, L. J., and Hu, C. H.: *Osteochondritis of the Head of the Femur: Experimental Study*, *Arch. Surg.* **27**:645 (Oct.) 1933.

42. Erb, K. H.: *Beitr. z. klin. Chir.* **158**:337, 1933.

other mediums, suggesting that bone marrow might lessen the virulence of the cocci. Injury of the bone marrow by roentgen treatment resulted in marrow which lost the power of decreasing the virulence of staphylococci. The author believed that he had demonstrated bactericidal power of rabbit bone marrow in vitro. It might be that means of artificially increasing or lowering this resistance could shed light on the genesis of osteomyelitis.

*Delayed Callus Formation from Antiseptic Treatment of Wounds.*—Boerema,<sup>43</sup> using pigeons and hens, studied the effect of antiseptics on the healing of fractures. A 5 per cent solution of tincture of iodine or a 3 per cent solution of phenol was kept in contact with the fracture ends for three minutes after which the operative wound was sutured. A delay in callus formation was observed, when the antiseptics were used, in comparison with normal controls. This retardation in healing the author believed due to the effect of antiseptics on the specific bone building tissues, the cambium layer of the endosteum and the periosteum.

*Neutralization of Poliomyelitis Virus.*—Southby and McKie,<sup>44</sup> in an experimental investigation, showed that while the pooled serums of normal adults exhibited a definite neutralizing action for the virus of anterior poliomyelitis, this action had only from 30 to 40 per cent of the potency of convalescent serum. They also concluded that there was a definite immunologic difference between the various strains of virus.

*Infection and Vaccination in Tuberculosis.*—The conclusions drawn by Heimbeck<sup>45</sup> in his study of tuberculous infection in the commune hospital and among the population of Oslo were that allergy to tuberculosis was immunity to tuberculosis and that only a small number of persons contracted tuberculosis in childhood. Allergy indicated immunity whether produced by infection or by vaccination with BCG. Of 168 nurses vaccinated, 84 became allergic as indicated by the reaction to the Pirquet test. Of these 84 nurses, only 1 contracted tuberculosis. Of the other 84 nurses who did not become allergic through vaccination, 18 later had tuberculous infections. The author advocated repeating vaccination with BCG until allergy was produced.

*Lymphatic Drainage of Joints.*—Kuhns,<sup>46</sup> working with rabbits, found lymphatics present as abundant small vessels in the articular tissues. They were most numerous just beneath the epithelial-like layer of the synovial membrane. The lymphatic drainage of the lower extremity was through the so-called deep lymphatics to the popliteal,

43. Boerema, I.: Arch. f. klin. Chir. 176:666, 1933.

44. Southby, R., and McKie, M.: M. J. Australia 2:404, 1933.

45. Heimbeck, J.: Med. Klin. 29:1731, 1933.

46. Kuhns, J. G.: Lymphatic Drainage of the Joints, Arch. Surg. 27:345 (Aug.) 1933.

deep femoral and iliac lymph nodes. Inflammation in the synovial tissues resulted in a decreased ability on the part of the lymphatics to absorb material greater than molecular size. An apparent obliteration of the lymphatic vessels occurred when the inflammatory process was sufficiently severe or long continued.

*Experimental and Clinical Observations on Tonus of Striated Muscle after Sympathectomy in Spastic Paralysis.*—Kasumov<sup>47</sup> reported observations made on dogs in which a lumbar sympathectomy was followed by an operatively produced spastic paralysis. The sympathetic trunks were resected from the diaphragm to the first sacral segment on one side. Twenty-four days later the anterior motor roots were cut on both sides: from the fourth to the seventh lumbar and the first and second sacral. The muscle action was studied kymographically for several months. The muscles were weaker at first on the side on which sympathectomy was performed, and contractures developed much later on this side. Sympathectomy was performed on 18 children with spastic paralysis. Six showed considerable improvement, 9 slight improvement. The author believed sympathectomy was of value in weakening muscular rigidity. He advised its use in conjunction with other therapeutic measures.

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47. Kasumov, G.: *Sovet. khir.* 4:503, 1933.

## CLINICAL USE OF PENTOBARBITAL SODIUM AS A PREANESTHETIC AGENT

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CLEVELAND

Pentobarbital sodium, because of the rapidity with which sedation or hypnosis occurs after its oral administration and the short duration of its action owing to its rapid destruction in the body, appeared to be one of the most promising of the newer fixed hypnotics for preanesthetic medication from both an experimental (Fitch, Waters and Tatum;<sup>1</sup> Barlow, Duncan and Gledhill;<sup>2</sup> Kleindorfer, 1932) and a clinical standpoint (Lundy;<sup>3</sup> Wilcox;<sup>4</sup> Magill<sup>5</sup>). The marked relief from apprehensiveness and the practical absence of disagreeable associated actions, such as preoperative excitement and respiratory or circulatory depression when used in effective dosages, suggested a trial of this agent for surgical premedication in man.

The use of pentobarbital sodium in the surgical service of the University Hospitals was begun in April 1932. The procedures established by experience have become routine, and this type of premedication at the present time is administered in approximately 65 per cent of all surgical cases requiring premedication. The present report is based on more than 700 records of surgical anesthesia and a detailed study of 455 records chosen at random from the entire group. The age of the patients ranged from 3 months to 81 years. The nature of the operative procedures in the series studied, grouped as to region in terms of percentages of the total, are as follows: head, 3.55; face, 8.66; neck, 10.21; chest, 9.19; breast, 6.44; back, 1.78; abdomen, 18.43; pelvis, 22.87, and extremities 18.87. The data obtained are considered sufficient to

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1. Fitch, R. H.; Waters, R. M., and Tatum, A. L.: *Am. J. Surg.* 9:110, 1930.
2. Barlow, O. W.; Duncan, J. E., and Gledhill, J. D.: *J. Pharmacol. & Exper. Therap.* 41:367, 1931.
3. Lundy, J. S.: *Anesth. & Analg.* 9:210, 1930.
4. Wilcox, W.: *Brit. M. J.* 1:266, 1931.
5. Magill, I. W.: *Lancet* 1:74, 1931.



establish the effects of the pentobarbital-morphine premedication sequence as to dosage of the hypnotic in relation to age and sex, and the nature of anesthesia produced with different types of supplementary anesthetics in relation to the type of operation and postoperative reactions.

#### PROCEDURE

The premedication varied somewhat with the nature of the operation, condition of the patient and the supplementary anesthetic to be administered. The usual sequence (in 70 per cent of the series) was as follows: Pentobarbital sodium ( $1\frac{1}{2}$  grains [0.09 Gm.]) was administered in a capsule on the evening preceding the operation in order to assure a restful night. The following morning, two hours before the scheduled time for the operation  $1\frac{1}{2}$ , 2 or 3 grains (0.09, 0.12 or 0.18 Gm.) of pentobarbital sodium (the dose gaged by the age and condition of the patient and the surgical indication) was administered orally. One hour later an equal dose of pentobarbital sodium was given orally with morphine ( $\frac{1}{8}$  grain [11 mg.]) and atropine ( $\frac{1}{150}$  grain [0.4 mg.]) hypodermically. The total amount

TABLE 1.—*Anesthetic Supplements and the Frequency with Which They Were Administered*

Anesthetic	Number of Cases	Percentage of Series
None.....	2	0.44
Local.....	90	19.98
Local and nitrous oxide and oxygen.....	2	0.44
Local and nitrous oxide, oxygen and ether.....	3	0.66
Snarl.....	8	1.77
Ether (drop).....	15	3.31
Ether (vapor).....	16	3.55
Nitrous oxide and oxygen.....	24	5.33
Nitrous oxide, oxygen and chloroform.....	1	0.22
Nitrous oxide, oxygen and ether.....	294	65.27

of the hypnotic administered on the morning of the operation was 3 grains or less in 51.3 per cent and more than 3 grains ( $4\frac{1}{2}$  to 9 [0.29 to 0.58 Gm.]) in the remaining 48.7 per cent of the patients. The optimal amount appears to be from 3 to 5 grains (0.3 Gm.). Patients subjected to operation on the thyroid gland or the gallbladder reacted better to large than to small doses. Full doses of morphine ( $\frac{1}{4}$  grain [16.2 mg.]) were administered, usually in combination with small doses of the hypnotic, only when indicated by the condition of the patient or by the nature of the surgical case. Approximately one half the patients who were to undergo operation on the breast and two thirds of those who were to undergo operation on the gallbladder were medicated with maximal doses of morphine.

The observations obtained with different doses of pentobarbital sodium with each type of supplementary anesthetic included: the pulse rate, the respiratory rate, and the blood pressure before and after premedication, during and after anesthesia, the duration of the operation and of the period of postoperative sleep (to return of consciousness); postoperative nausea; emesis, restlessness and the urinary findings both before and after the operation. The respective effects of morphine ( $\frac{1}{8}$  grain) and of different doses of pentobarbital sodium and morphine ( $\frac{1}{8}$  grain) on the respiratory minute volumes were determined for a small group. The patients were questioned during convalescence as to the presence or absence of amnesia and their general impressions. The anesthetic supplements and the frequency with which they were administered are shown in table 1.

The data were tabulated according to sex and type of operation, but differed so negligibly (with the exception of the gynecological, gallbladder, thyroid and cerebral groups) that all data with these exceptions are presented as a single group, and have been subdivided only as regards age, dosage of pentobarbital sodium and supplementary anesthetic. The main group includes all patients within the age limits of 18 and 60 years (fig. 1). The smaller groups include (a) ages below 18, (b) from 18 to 39, (c) from 40 to 59 and (d) more than 59 years (fig. 2). The data as illustrated in the figures represent medians, and with the exception of the time of operation and post-operative sleep (in hours) are expressed as percentage changes from the original normal observations.

#### OBSERVATIONS BEFORE OPERATION

On arrival at the operating room (following medication with the pentobarbital sodium-morphine sequence), 24 per cent of the patients were asleep, 68 per cent were drowsy, analgesic and uninterested in any procedure; the remaining 8 per cent showed some inebriation and moved slightly when disturbed. With a total dose of 6 (0.38 Gm.) or more grains of pentobarbital sodium patients were invariably asleep. Approximately 1 of 5 showed some conjunctival congestion which persisted for about one half hour. This reaction is probably comparable to the similar condition observed in acute alcoholism, and occurs with regularity in animals after intravenous injections of the barbiturates (Richter and Oughterson;<sup>6</sup> Barlow<sup>7</sup>).

*Respiration.*—The normal respiratory rate was unaltered by pre-medication. Individual observations varied within a range of  $\pm 10$  per cent (from one to two respirations per minute). The respiratory volume, measured with a Bohr gas-meter before and after medication, was reduced slightly by pentobarbital and morphine. The change noted was unimportant and was similar in magnitude to that occurring during sleep. Morphine alone in a dose of 1/6 grain occasionally slightly increased, but usually diminished, the minute volume from 3 to 5 per cent. Medication with pentobarbital (3 grains) and morphine (1/6 grain) resulted in a 2 to 7 per cent depression. Following medication with larger amounts of the hypnotic (6 grains) and morphine (1/6 grain), a decrease in the minute volume, from 8 to 16 per cent (median 10), was noted.

*Pulse Rate.*—The pulse rate varied within a range of  $\pm 7.5$  per cent of normal. The majority of changes noted occurred in patients medicated with 3 grains or less of the hypnotic, and probably indicate

6. Richter, H. G., and Oughterson, A. W.: *J. Pharmacol. & Exper. Therap.* 46:335, 1932.

7. Barlow, O. W.: Unpublished data.

a slight insufficiency of such doses. The median data indicate that a slight rise in pulse rate occurs after medication with morphine and pentobarbital sodium.

*Blood Pressure.*—The blood pressure in the majority of patients was unchanged. However, oscillations on either side of normal were

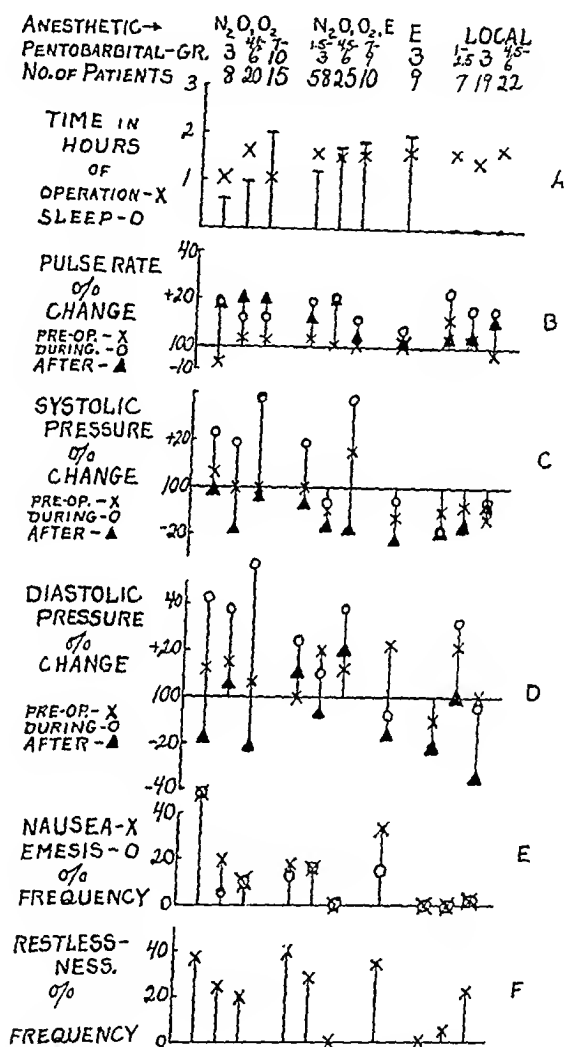


Chart 1.—The data massed according to the anesthetic supplements that were used. In all the charts the symbols  $N_2O$ ,  $O_2$ ,  $N_2O, O_2, E$ ,  $E$  and  $L$  at the top represent the anesthetic supplements nitrous oxide and oxygen, nitrous oxide, oxygen and ether, ether and a local anesthetic; the numbers in the second line the grains of pentobarbital sodium administered, and those in the third line, the number of patients whose anesthetic records are tabulated below.

observed, usually in conscious patients. If the patients were asleep, a decrease was noted. The degree of change was independent of the hypnotic dosage. Hypertensive patients usually showed the systolic change of sleep. The diastolic pressure was either unaltered or rose

with a median increase of from 3 to 7 per cent. The diastolic rise was most frequently observed in patients under 40 years of age, and a fall of from 5 to 10 per cent occurred in patients more than 59 years of age.

*Nature of the Anesthesia.*—Apprehensiveness on the part of the patient was rarely encountered following medication with pentobarbital

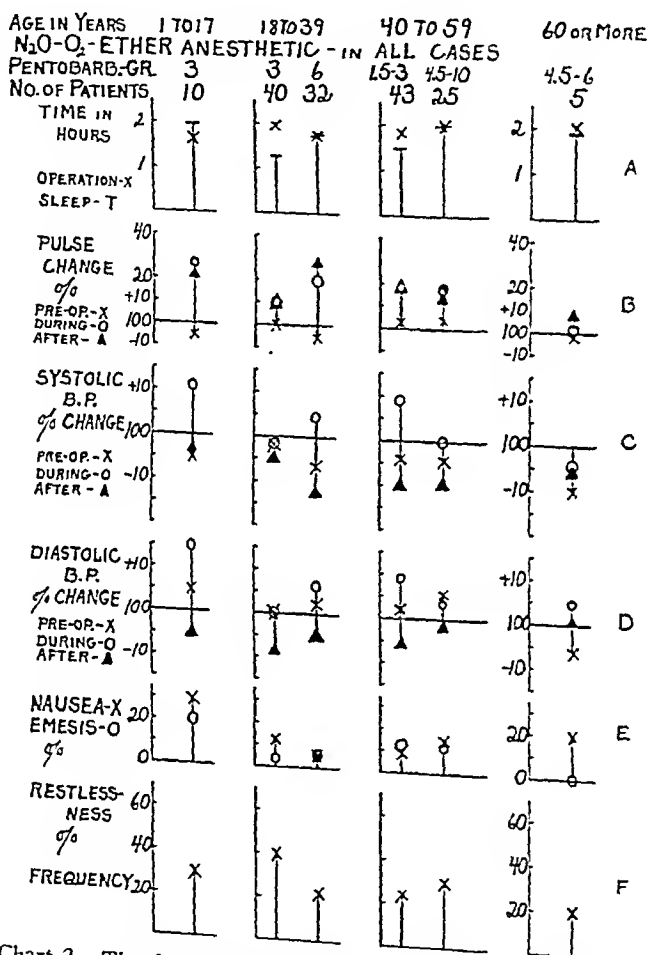


Chart 2.—The data massed according to the ages of the patients.

sodium (2 or more grains) and morphine. The patients were asleep, uninterested in any procedure or cooperative. The period of induction was uneventful and independent of the nature of the anesthetic supplement. The quantity of the anesthetic required during the course of anesthesia was significantly less than that usually required with morphine and similar supplements alone. Surgical anesthesia was usually established within from three to six minutes and easily maintained. The most pleasing features of this anesthetic sequence are the ease of

establishment and maintenance of anesthesia, the wider margin of safety and the apparent absence of respiratory depression. With maximal doses of the hypnotic (from 6 to 9 grains), respiratory depression was observed exceptionally. Such reactions were due either to overmedication with morphine ( $\frac{1}{2}$  grain) or to the condition of the patient, i. e., secondary anemia or a limited pulmonary surface. Under such conditions nitrous oxide and oxygen mixtures containing higher percentages of oxygen were sufficient to maintain good color as well as surgical anesthesia.

From 85 to 96 per cent of the anesthetics were good, the remainder fair. Poor anesthetics were infrequent (less than 0.5 per cent), but were most frequently observed with ether as the supplement. Anesthetics with nitrous oxide and oxygen, when preceded by the administration of morphine and pentobarbital sodium in doses of less than 3 grains, were somewhat less satisfactory than with from 3 to  $4\frac{1}{2}$  grains. So far as age was concerned, patients ranging from 1 to 39 years reacted equally well; i. e., anesthesia was satisfactory; it was somewhat less so with an age range of from 40 to 59 years and least satisfactory with aged patients (more than 59 years of age). Patients with gynecological or thyroid conditions (especially aged persons) reacted somewhat less satisfactorily than other groups to the premedication, gas-oxygen sequence. The degree of relaxation obtained in these two groups of patients was insufficient, necessitating the use of either maximal doses of pentobarbital sodium or the addition of ether to the nitrous oxide and oxygen mixture. Nitrous oxide, oxygen and ether was the anesthetic supplement of choice for the average patient.

#### OBSERVATIONS DURING AND FOLLOWING OPERATION

*Changes in the Pulse Rate.*—The median changes in pulse rate in the massed age group (from 18 to 60 years) observed preoperatively (after medication but preceding the administration of the supplementary anesthetic), during the course of anesthesia and on return to bed are illustrated (by symbols) in terms of the per cent variation from normal (100 per cent) in figure 1 *B*. Similar observations for different age groups are illustrated in figure 2 *B*.

**Nitrous Oxide and Oxygen:** The pulse rate increased from 15 to 27 per cent above normal during the course of anesthesia. The degree of rise was greatest with small to intermediate doses and least with maximal doses of pentobarbital sodium. The factor of dose does not appear significant, however. So far as age is concerned, patients ranging from 1 to 39 years reacted similarly. Minimal changes occurred in aged patients. Postoperatively, pulse rates fell slightly with small to medium doses, but rose above the operative peak with maximal doses. The postoperative pulse rate in immature patients (fig. 2) increased

maximally and corresponded closely to that noted with maximal hypnotic doses in adults.

**Nitrous Oxide, Oxygen and Ether:** With small doses of the hypnotic, the pulse rate increased to a smaller degree (fig. 1) than with nitrous oxide and oxygen. Only young patients proved an exception. The differences were not of great significance, however. With larger doses of the hypnotic no differences between the two supplements were apparent. Postoperatively the pulse rate as a rule fell slightly toward normal (except in aged patients, in whom a further rise occurred), and with maximal doses was within 5 per cent of normal.

**Ether:** Changes in the pulse rate in adult patients during ether anesthesia or postoperatively were unimportant. A negligible rise occurred as a rule. With young subjects receiving minimal doses of the hypnotic and fractions of the adult dose of morphine, the preoperative pulse rate increased 15 per cent, and an equal further rise occurred during anesthesia. This maximal level persisted postoperatively.

**Local Anesthesia:** The changes in pulse rate noted during local anesthesia were moderate, and bore no apparent relationship to the hypnotic dose, irrespective of age; but no change was apparent in the small group of immature patients on whom data are tabulated. Postoperatively the pulse rates fell toward normal, and with aged patients the terminal values were from 5 to 15 per cent below normal.

**Blood Pressure.**—During the course of anesthesia oscillations (especially postoperatively) were greatest in the aged, intermediate in the young and least in the average group. The qualitative change in preoperative systolic pressure bore no relation to the amount of hypnotic administered, and was increased, unchanged or decreased. A slight fall (from 2 to 5 per cent) was the rule, and differed negligibly as to age except in the aged, in whom changes were greatest. The oscillations observed may be attributed to individual variation or, more probably, to the relative physical state of the patients as reflected by their surgical requirements.

During the course of anesthesia, with all supplements except the local, the changes in systolic pressure were similar in direction, but quantitatively greater than the accompanying changes in pulse rate. With local anesthesia, the systolic pressure fell, but the degree of change was inverse to the rise in pulse rate. Postoperatively the pressure fell to or below normal, bore little or no relationship to the hypnotic dose or to the age of the patients, but increased with the several anesthetic supplements in the following order: nitrous oxide and oxygen, nitrous oxide, oxygen and ether, local, and ether.

The diastolic pressure varied preoperatively from a slight fall to a 20 per cent increase; the general picture as indicated by the median

reaction was a 10 per cent increase. The changes noted were unrelated either to the age of the patients or to the degree of premedication. During the course of anesthesia with either nitrous oxide and oxygen or nitrous oxide, oxygen and ether, the general blood pressure increased, but the diastolic change was greater than the systolic, owing probably to the moderate anoxemic factor. Under ether anesthesia the fall of the diastolic exceeded that of the systolic pressure. Under local anesthesia the oscillations were of greater magnitude than with other supplements. Postoperatively, the diastolic level fell from the values established during anesthesia to a level from 5 to 10 per cent below the preoperative figure. The degree of change was usually inverse to the degree of change which occurred during the course of anesthesia. No clearcut relationship could be observed between the degree of change and age, but the fall noted in the group receiving a local anesthesia was of greater magnitude than with the other anesthetic supplements.

*Respiration.*—Respiratory changes were unimportant. The rate was unaltered, although a slight decrease in volume occurred, as indicated by the minute volumes. During the course of anesthesia the respiratory rate increased from 30 to 60 per cent with a moderate compensatory decrease in volume. The changes observed differed insignificantly with the several anesthetics, except with the local anesthetics, with which a change of from 15 to 20 per cent occurred. The respiratory center was sensitive to carbon dioxide throughout anesthesia. Cyanosis occurred rarely and was not observed under conditions of proper premedication. The color of the patient was easily controlled by decreasing the percentage of nitrous oxide and increasing that of oxygen in the gas mixture. Aged patients showed a greater degree of depression and a smaller degree of stimulation during the course of anesthesia than younger patients. Postoperatively, respiratory rates and minute volumes returned either to normal or to the level of premedication sleep.

*Duration of Postoperative Sleep.*—The duration of postoperative sleep (solid line, section A, figs. 1 and 2) varied widely in individual patients, i. e., from a few minutes to ten hours. A rather remarkable variation existed in patients of comparable age, sex and general condition and subjected to the same operative procedure with the same premedication therapy. Lethargic persons invariably slept longer than excitable patients. The severity of the surgical procedures, the period of operation and the dosage of the hypnotic as well as the nature of the anesthetic supplement must be considered in explaining the observed variations in the time required for the return to consciousness postoperatively. The surgical procedures and the period of the operation as well as the narcotic dosage were for all general purposes constant, so that only the anesthetic supplements and the hypnotic need be taken

into consideration. The median time of sleep in the group receiving nitrous oxide and oxygen grossly parallels the dose of the hypnotic: i. e., with minimal doses the duration of sleep was forty minutes and with maximal doses two hours. With a nitrous oxide oxygen and ether supplement or an ether supplement the same order holds, but the differences with the three dosages of pentobarbital sodium are less significant. With these two supplements the additional postoperative depression caused by the ether per se was apparent, in that the time of sleep was shortest with nitrous oxide and oxygen, longer with nitrous oxide, oxygen and ether, and longest with ether, although the premedication was the same in each case. With local anesthesia the patients were rarely unconscious when they returned to their room. The absence of postoperative depression with local anesthesia is partly explained by the absence of additive depression from the hypnotic and anesthetic. In addition, the depression caused by premedication per se was probably diminished as a consequence of the known hypnotic-local anesthetic antagonism.

The amount of pentobarbital sodium required for the production of a unit reaction appears to be dependent, primarily, on the general condition of the patient and, secondarily, on age. For example, the youngest patient (3 months of age) in the series was medicated with 1 grain of pentobarbital sodium, while a 50 year old patient weighing more than ten times as much as the infant received 3 grains. Both patients were subjected to the same supplementary anesthetic and surgical procedures with equally satisfactory results. The observed relation between the effectiveness of the hypnotic and age, as indicated by the period of postoperative sleep is illustrated in figure 2. The order of sensitivity from greatest to least was: ages 1 to 17, 60 years or more, from 40 to 59 years and the group from 18 to 39 years.

*Restlessness.*—A few patients of the group of more than 700 receiving surgical anesthesia medicated with minimal doses of pentobarbital sodium became somewhat excited on arriving at the operating room instead of being quieted. Such reactions were exceptional. These patients were less cooperative than is normal and responded less satisfactorily to local anesthesia. Such reactions may be corrected by the production of a slight analgesia with nitrous oxide. Postoperative restlessness occurred in a certain percentage of all types of patients (F, fig. 1). It varied in frequency of occurrence with the hypnotic dose administered, but particularly with the type of patient. Apparently the frequency was somewhat less with moderate than with light doses, and might have been entirely absent with large doses. With the exception of those receiving ether and local anesthetics, the degree and frequency of occurrence were inverse to the duration of postoperative sleep. The restless movements, when present, were purposeless, and ranged



in degree from barely perceptible to marked movements which required at times either individual care for a few hours or, rarely, actual restraint. Morphine administered postoperatively was required by approximately one half of the restless patients and effectively controlled the reaction. Patients in the gynecological, thyroid or gallbladder groups were more prone to show postoperative restlessness than patients undergoing other types of surgical procedure.

The frequency with which restlessness occurred during the post-anesthetic stage with different age groups is illustrated in section *F*, figure 2. Athetoid movements were most frequent in subjects under 18 years of age, decreased in frequency in succeeding age groups and were least frequently noted in aged patients. Correlation of restlessness with the nature of the supplementary anesthetic indicated that the order of frequency from greatest to least was: ether, nitrous oxide, oxygen and ether; nitrous oxide and oxygen, and local anesthesia. The reaction noted following pentobarbital sodium and local anesthesia differed in one respect from that noted with the other supplements. With nitrous oxide and oxygen, for instance, the frequency decreased with increasing doses of hypnotic, but with the local anesthetics restlessness was absent with minimal doses and gradually increased with increasing doses of the hypnotic. Restlessness occurred exceptionally after the administration of the hypnotic-local anesthetic sequence in the age group of from 3 to 50 years, but occurred in 40 per cent of patients 60 or more years of age.

*Nausea and Emesis.*—These occurred postoperatively in all groups receiving supplementary anesthetics with the exception of those receiving local anesthesia. It appears therefore that pentobarbital sodium, independent of the dose, does not produce nausea or vomiting. Emesis occurred less frequently than nausea, but occasionally a small amount of mucus was vomited in the absence of nausea. The frequency of occurrence, although significantly less than that reported by Shaw,<sup>8</sup> was highest with ether, and apparently decreased with the other supplements as well as with increasing doses of the hypnotic. The frequency was somewhat greater in the group receiving nitrous oxide and oxygen than in those receiving nitrous oxide, oxygen and ether. This apparent paradox is unexplained, but may be related to the duration of post-operative depression. So far as age was concerned (fig. 2), the frequency of occurrence of nausea and emesis was greatest in the extremes of age and least frequent in the group from 18 to 39 years.

*Urinary Findings.*—Albumin was demonstrable in approximately 10 per cent of the first postoperative specimens, either voided spontaneously or obtained by catheter, and unless present on admittance disappeared after the first convalescent day. The majority of the

8. Shaw, R. W.: *Lancet* 2:1435, 1932.

patients were females and less than one third of the specimens were obtained by catheterization. It is probable therefore that albuminuria occurs less frequently than these data indicate, as less than 4 per cent of the specimens of urine from males were positive for albumin postoperatively. Casts were rarely observed postoperatively, and when present were likewise noted preoperatively. The output of urine was reduced proportionately to the intake of water. Retention was apparently uninfluenced by the sequence of premedication used.

*Period of Amnesia.*—Complete amnesia occurred for from 5 to 8 hours postoperatively in approximately one third of the patients premedicated with 3 grains or less of pentobarbital sodium. The amnesia began from ten to thirty minutes after the administration of the capsule. Amnesia was partial; i. e., the memory was confused, in an additional 30 per cent. No amnesia was observed in the remaining 40 per cent. With larger doses of the hypnotic ( $4\frac{1}{2}$  or more grains) amnesia was complete in 75 per cent of the patients and persisted for from nine to twelve hours and, exceptionally, for from eighteen to twenty-one hours postoperatively with maximal doses. The remaining 25 per cent had an imperfect memory for a period of several hours postoperatively. Following medication with from 9 to 10 grains (0.64 Gm.) of the hypnotic it was difficult to arouse the patients, who slept from eight to sixteen hours after being returned to bed.

The patients medicated with the hypnotic-narcotic-supplementary anesthetic sequence were pleased, having no disagreeable after-impressions, and being oblivious to any reactions that might occur in the postoperative period. From the standpoint of the patients, the most pleasing supplementary anesthetics were nitrous oxide and oxygen and a local anesthetic. Ether was least satisfactory.

#### OBSERVATIONS ON SPECIAL SURGICAL GROUPS

*Nature of the Anesthesia.*—The course of anesthesia was somewhat less satisfactory in patients in the thyroid and gynecological groups than in other surgical groups, in spite of heavy premedication with pentobarbital sodium. Poor anesthetics were more frequent, and greater difficulties were encountered in maintaining an even anesthesia. For the average patient who was to undergo an operation on the thyroid gland, the optimal premedication sequence appeared to be pentobarbital sodium, from 6 to  $7\frac{1}{2}$  grains, morphine,  $\frac{1}{6}$  grain, and atropine, ( $\frac{1}{150}$  grain). Nitrous oxide and oxygen constitutes a satisfactory supplement. Aged patients responded less satisfactorily, however. The optimal premedication dosage for patients in the gynecological group appeared to be from 3 to  $4\frac{1}{2}$  grains of the hypnotic. Poor anesthetics were somewhat more frequent with heavier premedication, but postoperative reactions were less frequently observed after large than after

small doses of the hypnotic. Patients undergoing operations on the gallbladder responded best to from 6 to 7½ grains (0.48 Gm.) of pentobarbital sodium, followed by morphine, (¼ grain), supplemented with nitrous oxide, oxygen and ether. Aged patients responded especially well to this combination. With smaller doses of the hypnotic and full doses of morphine, anesthesia was least satisfactory. The efficiency of ether preceded by from small to moderate doses of the

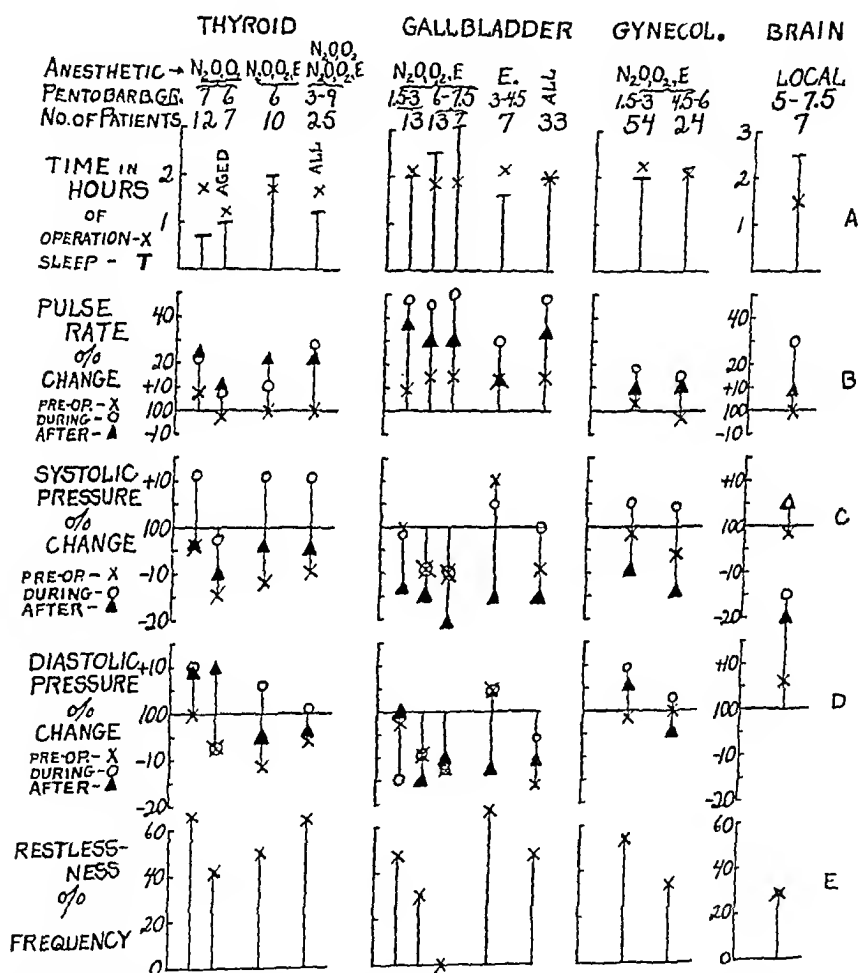


Chart 3.—The data on four special surgical groups, massed according to the types of surgical procedures involved.

hypnotic was intermediate between the two gas anesthetics used. The reaction of patients in the cerebral group to large doses of pentobarbital sodium and local anesthesia was excellent.

**Pulse Rate.**—The changes in pulse rate (fig. 3) noted preoperatively were insignificant in the thyroid, gynecological or cerebral groups. A 14 per cent rise was noted in the cholecystectomized group. During the course of the anesthesia or postoperatively, oscillations of the pulse

were of no greater magnitude than described for the general type of case (fig. 1). Oscillations were significantly greater in the group undergoing operation on the gallbladder than in any other type of case. During the course of the operation the pulse rate increased from 30 to 50 per cent and remained from 15 to 35 per cent above normal post-operatively.

*Blood Pressure.*—The blood pressure was little altered following premedication, although a decrease of approximately 10 per cent was noted with maximal doses. Systolic and diastolic changes were parallel. Occasionally a marked fall in blood pressure occurred which might have been due to individual susceptibility, in which case the dosage would probably have little influence. Such falls are so exceptional that the reaction should not limit the use of the method, especially, as it is not certain whether they were due to the drug or to some other unrecognized cause.

*Respiratory Changes.*—The changes observed in the special surgical groups did not differ significantly from those described for the massed group. The patients in thyroid and gallbladder groups although medicated with maximal doses of the hypnotic, as well as with full doses of morphine in the latter group, showed no greater alterations in the respiratory rate than were observed in other surgical groups. Patients in those groups appeared most resistant or tolerant to heavy premedication.

*Period of Postoperative Sleep.*—Patients with hyperthyroidism recovered consciousness more rapidly than any other type of surgical patient. Aged subjects recovered somewhat less rapidly than those in the age range of from 30 to 45 years. The duration of sleep differed significantly with different anesthetic supplements; i. e., with similar premedication postoperative sleep was at least twice as long with nitrous oxide, oxygen and ether as with nitrous oxide and oxygen. Patients with gynecological and gallbladder diseases slept somewhat longer than other surgical groups (with the exception of the brain group), owing probably to the greater severity of the surgical procedures. The long sleep following operations on the brain (in the absence of morphine) was in contrast to the reaction of other groups medicated with the hypnotic local anesthetic sequence, since, with the exception of the brain group, the period of postoperative sleep was rarely noted as independent of the hypnotic dosage.

*Restlessness:* Postoperative restlessness occurred in 64 per cent of the lobectomized group of patients. The frequency bore little relation to the hypnotic dose, but this reaction was more frequent following nitrous oxide and oxygen than after nitrous oxide, oxygen and ether. The lesser frequency together with the longer period of postoperative sleep with the latter supplement suggests that restlessness bears some

relation to the degree of postoperative depression. The high metabolic rate and nervous instability of such patients are probably of greater importance, however. Patients with gallbladder conditions were somewhat more restless than the general average, especially with small doses of the hypnotic. The frequency of restlessness decreased with increasing doses of the hypnotic, and none was noted in the aged group of patients.

The use of ether as the anesthetic supplement appeared to exaggerate the frequency with which restlessness occurred after comparable doses of the hypnotic and the other supplements. Patients in the gynecological group were somewhat more troublesome than those in other surgical groups from the standpoint of nursing. The data suggest that the dose of the hypnotic was insufficient, the major portion of the patients having received 3 grains or less. In this group restlessness was frequent. With larger doses (from  $4\frac{1}{2}$  to 6 grains) the factor of restlessness was no greater than in other surgical groups. This hypothesis appears substantiated in that postoperative restlessness has become relatively unimportant since pentobarbital (acid) was substituted for the sodium salt of the same preparation in the gynecological service. The lower frequency of postoperative movements noted after medication with the acid form of the hypnotic indicates that the dosage used previously was insufficient (the molecular weight of the acid is 10 per cent less than that of the sodium form) or that a longer postoperative depression occurs with the premedication sequence used at the present time. This point is being studied.

*Nausea and Vomiting.*—Nausea was recorded in 11 per cent of patients following thyroidectomy but emesis did not occur. The frequency was greater following the use of a nitrous oxide, oxygen and ether supplement. From 10 to 18 per cent of the gynecological patients were nauseated, and less than 10 per cent vomited postoperatively. Nausea did not occur in the group but emesis was observed in 1 case. The gallbladder group differed from the other group, in that nausea was much more frequent. The frequency with which nausea occurred bore little relation to the dose of the hypnotic, and, contrary to experience in all other surgical cases, was more frequent in the aged than in the younger patients. The frequency was four times as great after ether than after nitrous oxide, oxygen and ether, even though the premedication sequence was constant. Emesis occurred one-half as frequently as nausea. The greater frequency with which nausea and emesis occurred in the gallbladder series was probably related to the nature of the organic disturbance.

*Urinary Findings:* Changes following anesthesia were unimportant. The urinary findings in the cerebral group of patients were negative. No casts were observed in the urine of the gynecological group, and, although transient albuminuria was occasionally observed (in the first postoperative specimen only), the data are of negative value only, owing

to the infrequency with which catheterized specimens of urine were obtained. The presence of albumin and casts was noted much more frequently (normal specimens) in the thyroid and gallbladder groups, and especially in aged patients, than in the other groups. The frequency of the occurrence of casts was the same both preoperatively and postoperatively. The frequency and degree of albuminuria postoperatively were exaggerated temporarily by anesthesia, but it is improbable that premedication procedures contributed to the temporary renal changes noted.

#### EXCEPTIONAL REACTIONS IN ALL TYPES OF SURGICAL CASES

Unsatisfactory reactions of greater or less severity were noted in 3 per cent of the total number of case records studied in detail. These reactions were of three types: (1) a moderate fall in blood pressure during the preoperative period, (2) a moderate to severe fall in blood pressure during the course of the operation or during the postoperative period and (3) respiratory disturbances during the course of anesthesia.

The average fall of blood pressure in the first group, i. e., after medication but preceding the administration of the anesthetic, was 30 mm. of mercury. The pulse rate and respiratory rate were not significantly altered in 4 of the 5 patients included in this group. Four of the 5 subjects had been medicated with pentobarbital sodium ( $4\frac{1}{2}$  grains), morphine ( $\frac{1}{6}$  grain) and scopolamine ( $\frac{1}{150}$  grain). The preponderant frequency with which reactions of this type occurred in the presence of scopolamine does not appear to be a coincidence, since reactions occurred in 20 per cent of all patients similarly medicated. The use of scopolamine in the presence of pentobarbital sodium and morphine is certainly of questionable value. Three of the 5 patients were treated with ephedrine ( $\frac{3}{4}$  grain) during the course of the operation. The patients were returned to bed on conclusion of the surgical procedures in good condition.

The second type of reaction, i. e., fall in blood pressure during or immediately following completion of the operation, was observed in 4 patients. The degree of change was insufficient in 2 cases to require treatment, but the other 2 patients showed signs of surgical shock. Satisfactory recoveries occurred in both patients following the administration of ephedrine in one and an infusion of dextrose intravenously in the other.

Three patients showed respiratory disturbances during the course of anesthesia. The first patient became cyanotic shortly after anesthesia was established, owing to faulty induction. Caffeine sodium benzoate was administered. The subsequent anesthesia was uneventful, and in spite of a long pelvic operation the patient was returned to her room in good condition. In a second patient, the induction of anesthesia with the usual nitrous oxide and oxygen mixtures was followed shortly by

marked cyanosis. This patient had received premedication with pentobarbital sodium (6 grains), morphine ( $\frac{1}{2}$  grain) and atropine ( $\frac{1}{150}$  grain). The reaction was considered due to the more than average sensitivity of the subject to morphine, i. e., to overmedication with the narcotic in the presence of large doses of the hypnotic. Similar reactions following the administration of sodium amytal and morphine under comparable conditions have been reported clinically by Fitch and his co-workers<sup>1</sup> and Zerfas<sup>9</sup> and observed experimentally by Barlow. The third patient had severe secondary anemia and became cyanotic during the course of anesthesia with nitrous oxide and oxygen. The last 2 patients received no treatment other than an increase in the percentage of oxygen in the gas mixture. The cyanosis was relieved without altering the character of the anesthesia.

*Pulmonary Complications.*—Following the use of the pentobarbital sodium-morphine general anesthetic sequence, pulmonary complications

TABLE 2.—Complications

Anesthetic Sequence	Number of Cases	Complications	Pulmonary Complications, per Cent of Series
Pentobarbital sodium and morphine, supplemented with nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether.....	378	1	0.26
Morphine and atropine, supplemented with nitrous oxide, oxygen and ether.....	505	11	2.18
Ether .....	185	5	2.7
Spinal .....	46	3	6.5
Spinal and nitrous oxide, oxygen and ether.....	8	2	25.0
Local anesthetic .....	341	3	0.88

were significantly less frequent than with other types of anesthesia. The frequency with which complications were observed during 1932 in a carefully controlled group of patients in the general surgical service is indicated in table 2. The data appear clearcut. We believe, however, that in view of the small total number of pulmonary complications noted the figures must be supplemented or confirmed before this point can be definitely established.

#### SUMMARY AND CONCLUSIONS

The present report is a review of the records of more than 700 surgical anesthetics in which the patients received premedication with pentobarbital sodium in doses ranging from  $1\frac{1}{2}$  to 9 grains (optimal, from 3 to  $4\frac{1}{2}$ ), morphine and atropine supplemented with several types of general anesthetics.

9. Zerfas, L. G.: Brit. M. J. 2:897, 1930.

Preanesthetic medication with pentobarbital sodium and morphine reduces or eliminates apprehensiveness so that the patient with rare exceptions arrives in the operating room either asleep (depending on the hypnotic dose administered and the relative sensitivity of the patient) or wholly uninterested in any mechanical or anesthetic procedure. The pulse may be unchanged or may oscillate on either side of normal, but an increase of from 1 to 4 per cent occurs as a rule. The changes in blood pressure and pulse rate preoperatively bear an inverse relation; i. e., a rise in the pulse rate is usually coincident with a slight decrease in the blood pressure. The median variation in blood pressure is within a range of plus or minus 7 per cent. The circulatory changes observed following premedication were not significantly divergent in different surgical types with the exception of patients with thyroid and gallbladder conditions. In the two exceptional groups oscillations were more variable and slightly greater in degree. The respiratory rates were unaltered by premedication. The respiratory volume as indicated by recorded changes in the minute volume was reduced insignificantly, and the decrease noted even with maximal doses of the hypnotic (and narcotic) was within the normal range of changes occurring during sleep.

The induction of anesthesia was smooth, distinctly shorter in point of time than in the absence of the hypnotic, and anesthesia could be established and maintained with ease with smaller quantities of the supplementary anesthetic than are required without such premedication. From 85 to 96 per cent of the anesthetics were good; the remainder were "fair." Poor anesthetics were infrequent. Anesthetics were least satisfactory in patients in the thyroid and gynecological groups. The hypnotic-narcotic-supplementary anesthetic sequence was most satisfactory in young and least satisfactory in aged patients. Nitrous oxide, oxygen and ether was the supplementary anesthetic of choice.

The pulse rate increased from 10 to 20 per cent during the course of anesthesia, and diminished somewhat from the operative peak immediately following the period of anesthesia. Changes in the pulse rate were maximal in young and minimal in aged patients; the changes observed in patients with surgical conditions of the thyroid and gallbladder were of greater magnitude than in other surgical types.

The blood pressure varied widely in exceptional cases during the course of operation, i. e., from 10 per cent below to 25 per cent above normal. In general, a rise of from 5 to 10 per cent above normal was observed with nitrous oxide and oxygen or nitrous oxide, oxygen and ether. With ether or local anesthesia the median pressure either decreased or increased slightly from the premedication level but, with the exception of the group undergoing operations on the brain, it remained below normal during the course of the operation. Systolic



and diastolic pressures, although qualitatively similar, differed markedly in exceptional instances. Postoperative pressures fell somewhat from the levels established during anesthesia.

Respiratory values during the course of anesthesia were difficult to evaluate. The rates increased significantly, and a moderate compensatory decrease in volume was observed. Disturbances were rare, and when such reactions occurred, were corrected by the adjustment of the anesthetic mixture of nitrous oxide and oxygen. Postoperatively, the respiratory rates and volumes returned either to normal or to the preoperative values.

The duration of postoperative sleep, although obviously influenced by the severity of the operative procedures to which the patients were subjected and the nature of the general anesthetic used, showed a fairly close correlation with the nature of the patient, i. e., with the general condition, metabolic level and nervous stability. Excitable persons (especially those with abnormal thyroid glands) require heavier premedication for a unit reaction than do lethargic patients. Body weight, according to this study, bore little relation to the degree of reaction of similar age and surgical groups to the same medication. No sexual differences were discernible. Age appears to be of some importance so far as the reaction to a unit dose is concerned. The observed susceptibility as judged by the duration of sleep postoperatively (type of operation and anesthetic being constant) appears to be in order from greatest to least: the immature age group (from 1 to 18); the aged (60 or more years), the 40 to 59 year group and least in the group from 19 to 39 years of age. The margin of safety appears wide, but caution should be observed if more than 9 grains is given, even with the sequence of divided doses used, and especially in the presence of morphine. Patients medicated with 9 to 10 grains are difficult to arouse; they sleep from eight to (exceptionally) sixteen hours postoperatively. Respiratory disturbances occur more frequently with maximal doses of the hypnotic in the presence of morphine, and occasionally the maintenance of a satisfactory color necessitates an increase in the percentage of oxygen in the gas mixtures as ordinarily used. Under such conditions the depth of anesthesia is uninfluenced by the accompanying decrease in the nitrous oxide in the mixture.

Purposeless movements ranging in severity from those just discernible to those requiring restraint were observed postoperatively in from 20 to 45 per cent of the patients medicated with pentobarbital sodium. The frequency was greatest in young and least in aged patients and decreased significantly with increasing doses of the hypnotic. Such movements may be entirely absent with maximal doses. Patients who had an operation on the thyroid or gallbladder were more restless postoperatively than other surgical types. Morphine effectively controlled these reactions.

No renal effects of the premedication sequence were noted. Any changes observed were easily explainable as minor reactions to the supplementary anesthetic and operative procedures, and in the main compared closely with preoperative findings.

The effectiveness of premedication with pentobarbital sodium appeared to be distinctly improved, especially as to the analgesia obtained, by the addition of small doses of morphine. Large doses of the hypnotic appear to be indicated in lobectomies and cholecystectomy. In the latter group full doses of morphine ( $\frac{1}{4}$  grain) are indicated in addition. In general, full doses of morphine should be used cautiously when more than 5 grains of pentobarbital sodium have been administered owing to occasional sensitivity of patients and the greater tendency of such medication to cause respiratory depression.

Amnesia beginning shortly after the administration of the hypnotic and persisting for from five to twelve or more hours postoperatively was observed in at least 75 per cent of the group of patients receiving 3 or more grains of pentobarbital sodium.

Undesirable reactions were observed preoperatively (before the administration of the anesthetic) in 5 cases and during or postoperatively in 7 cases. The preoperative change was a fall of blood pressure usually of moderate degree, although in 1 case the pulse became imperceptible. Four of the 5 patients received pentobarbital sodium, morphine and scopolamine. Three were treated with ephedrine during the course of the operation, but all were returned to bed in good condition. During the course of or following anesthesia a moderate to severe fall in blood pressure occurred in 4 patients. Two were in a state of shock and required treatment. Cyanosis was observed in 3 patients during the course of anesthesia, owing to improper medication for their physical condition. Operative procedures were not interrupted, and the color was controlled by increasing the percentage of oxygen in the mixture of nitrous oxide and oxygen.

# GAS BACILLUS INFECTION COMPLICATING LAPAROTOMY

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It is the purpose of this report to draw attention to gas bacillus infection<sup>1</sup> following laparotomy; this condition is manifested by a fulminating clinical course which may terminate fatally with startling rapidity. Failure to think of this complication, and the consequent omission of pertinent bacteriologic studies, may leave the surgeon mystified as to the actual cause of death. Frequently it is only when a post-mortem examination is performed that the situation is clarified.

Winter,<sup>2</sup> in 1889, reported 2 cases in which emphysema of the abdominal wall occurred after laparotomy. Eight years later Russell<sup>3</sup> reported 2 similar cases: one after uterine suspension and the other following a panhysterectomy. Subsequently, several reports of cases appeared in which gas gangrene was described as a complication of abdominal operations. It was reported after cholecystectomy, gastric and colonic resection, enterostomy and closure of a perforated peptic ulcer. However, the majority of infections with the gas bacillus occurred after appendectomy for gangrenous appendicitis.

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1. The gas bacillus, a frequent inhabitant of the intestinal tract, has been studied extensively in its relation to gangrenous appendicitis. Eleven cases of gas bacillus infection following operation for gangrenous appendicitis were reported by Simonds (*Studies in Bacillus Welchii*, New York, Rockefeller Institute, 1915). Bier (*Ann. Surg.* **81**:1117, 1923) and Ochsner and Schmidt (*S. Clin. North America* **5**:911, 1925) each reported a case of gas bacillus infection of the abdominal wall following appendectomy, with recovery. In 139 cases of appendicitis gas bacilli were isolated in 49 of the diseased appendixes, by Lanz and Tavel (quoted by Jennings: *New York M. J.* **117**:682, 1923). Hyde and Frederick (quoted by Jennings) found gas bacilli in 100 of 102 cases of acute appendicitis. Grigeroff (quoted by Russell<sup>3</sup>) noted that in normal appendixes, the aerobes and anaerobes were in equal proportions, or the aerobes predominated, whereas, in inflamed appendixes the strictly anaerobic bacilli were strikingly predominant. It is probable that the anaerobic gas bacilli take a significant part in the development, if not the causation, of acute appendicitis.

2. Winter, quoted by Russell.<sup>3</sup>

3. Russell: W. W.: Postoperative Emphysema of the Abdominal Wall, *Am. J. Obst.* **35**:517 (April) 1897.

Despite the widespread prevalence of the anaerobic bacilli, gas bacillus infection following laparotomy is relatively rare. The organisms have been identified in the discharge from abdominal drainage tracts, especially in cases of gangrenous appendicitis and acute cholecystitis. The gas bacillus has been isolated from the biliary tract and liver immediately after death. Gordon-Taylor and Whitby<sup>4</sup> reported the finding of *Bacillus Welchii* in cases of severe cholecystitis and in gangrenous gallbladders. This organism was isolated in 9 per cent of their cases of acute cholecystitis. In the routine examination of gallstones taken at autopsy these authors found *B. Welchii* in the nucleus of 13 per cent of the calculi. In view of the lack of correlation between the occurrence of gas bacillus infection and the extensive distribution of the organism, it is apparent that special conditions must obtain for its inception and development.

As has been demonstrated by Andrews and Hrdina,<sup>5</sup> the introduction of a bit of sterilized liver tissue into the peritoneal cavity of a rabbit will result in a gas bacillus infection. Evidently the introduction or formation of proteolytic substances produces the necessary conditions for the activation of the gas bacillus. Apparently the virulence of the organism is considerably enhanced in the presence of necrotic tissue.<sup>6</sup> The autolysis of devitalized tissue high in protein content produces substances which favor the appearance and rapid growth of anaerobic gas bacilli. Extensive involvement has occurred, however, in cases in which the amount of necrotic tissue originally present was almost negligible. When contamination occurs, it is probably due to the malignant toxin of the gas bacillus which provides by its necrotizing action the dead tissue indispensable to the development of the gas bacillus infection. The muscle is killed by a toxin-bearing edema which goes ahead of the bacillus. The gas may be a factor in opening up new channels, but without a necrosis-producing toxin the infection could not advance. The relative avirulence of the toxin of certain strains of

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4. Gordon-Taylor, G., and Whitby, E. H.: A Bacteriological Study of 50 Cases of Cholecystectomy with Special Reference to Anaerobic Infection, *Brit. J. Surg.* 18:78, 1930.

5. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* 52:61 (Jan.) 1931.

6. Reith (J. Bact. 12:367, 1926) reported the presence of *B. Welchii* in the muscular tissue of normal animals. Andrews, Rewbridge and Hrdina (*Surg., Gynec. & Obst.* 53:176, 1931) studied the production of *B. Welchii* infections in dogs by the injection of sterile liver extracts or bile salts. They showed that abscesses were produced which yielded *B. Welchii*, and they expressed the belief that the organism was already present in the tissues. They found that when large quantities of ground muscle tissue were placed in the abdominal cavity of experimental animals, invariably a gas bacillus infection resulted. This usually did not occur if the muscle was not ground.

anaerobic bacilli accounts in part for the cases in which the patient recovers. Furthermore, the heterogeneity of the group also is partly responsible for the varied clinical aspects and the different responses to serum treatment. Clinically it has been noted that the presence of streptococci, staphylococci and *Bacillus coli* results in an increased virulence of *B. Welchii*. Meleney and his associates<sup>7</sup> demonstrated with mixtures of *B. Welchii* and the common pyogenic organisms that the lethal dose in mice was considerably smaller than that of each organism alone. They expressed the belief that a definite synergistic action occurs.

The infection may begin in the muscle of the abdominal wall, the peritoneal cavity or the liver. The pathologic changes are the result of the toxemia alone or of the toxemia plus the presence of organisms and gas. When muscle is involved it becomes edematous, necrotic and crepitant. The "cooked meat" appearance is typical. Microscopically the muscle bundles appear necrotic; the sarcoplasm is dense and contracted, producing a space between it and the sarcolemma. This space is said to contain the toxin-bearing edema. The gas is found mainly along fascial planes. The liver shows marked parenchymatous degeneration, true toxic hepatitis, which may progress to widespread necrosis. Toxic nephritis is present. A constant feature is the extensive necrosis of the suprarenal glands. Similar toxic changes exist in practically all the other viscera. When the gas bacilli circulate in the blood stream, a characteristic infiltration of all tissues by gas occurs. The liver has a spongy, foamy appearance. On sectioning the preserved, fixed brain reveals a "Swiss cheese" appearance. Tremendous infiltration of all the tissues by gas bacilli takes place. The air bubbles may even appear to be lined with gas bacilli.

The clinical picture is one of overwhelming toxemia. Within from six to twelve hours after operation certain alarming signs may appear in a patient whose postoperative recovery has been proceeding satisfactorily. The blood pressure begins to drop slowly but steadily, and the pulse rate is accelerated correspondingly. The anxious, restless patient becomes semistuporous and finally lapses into coma. The skin and extremities are pale, cold and moist. The most striking phenomenon is the progressive increase in body temperature, reaching sometimes as high as from 108 to 110 F. Despite the usual antipyretic measures, the temperature does not fall. The combination of very high fever and pale cold skin signifies an extreme degree of peripheral vasoconstriction. Shock therapy produces little or no improvement. Examination of the

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7. Meleney, F. L.; Olpp, J.; Harvey, H. D. and Jern, H. Z.: Peritonitis; Synergism of Bacteria Commonly Found in Peritoneal Exudates, *Arch. Surg.* 25: 709 (Oct.) 1932.

wound may give negative results; however, if the infection involves the abdominal wall, crepitation may be elicited early. There is a marked diminution of the urinary output; complete anuria may occur. This may be accompanied by a deepening jaundice, and the icteric index may rise to 100 or more. The nonprotein nitrogen of the blood increases without a corresponding rise in the blood urea nitrogen. The urine has a high specific gravity and contains albumin and casts. The white cell count ranges between 20,000 and 30,000 per cubic millimeter.

Of late the literature has contained many reports describing the clinical aspects of postoperative "liver deaths." Heyd,<sup>8</sup> in discussing this entity, described three distinct types, one of which was similar to the clinical picture existing in gas bacillus toxemia and septicemia. As an illustration he described a patient in whom, shortly after operation, the temperature rose sharply. The pulse and respiratory rates became rapid. The patient became comatose and died in thirty-six hours. The postoperative course of our patients with gas bacillus infection was practically identical with this description by Heyd. In case 2 the diagnosis of acute hepaticorenal insufficiency was made, and it was not until the postmortem examination that the true cause of death was ascertained. The nonprotein nitrogen of the blood and the icteric index had both risen rapidly. The blood urea nitrogen was elevated to a lesser degree. The urinary output for the entire postoperative course was 7 ounces (198 Gm.). The similarity in the clinical manifestations of gas bacillus toxemia and those of hepaticorenal insufficiency indicates that actually acute insufficiency exists as a result of gas bacillus toxemia. The liver and kidneys in all our cases showed extensive parenchymatous changes. It is conceivable that in some cases the element of hepaticorenal insufficiency may be primary, with the gas bacillus infection engrafted on an already necrotizing, degenerating liver. That this secondary infection is possible and probable has been conclusively demonstrated by Mason<sup>9</sup> and by Andrews and Hrdina.<sup>5</sup> Especially in the cases of hepaticorenal insufficiency following traumatic pulpefaction of the liver, such as those reported by Heyd and Schutz<sup>10</sup> and others, it would seem that conditions are exceedingly favorable for the development and appearance of gas bacillus infection. Other than acute hepaticorenal insufficiency there are few conditions which simulate gas bacillus toxemia and septicemia. An acute, fulminating, streptococcic septicemia will occasionally produce

8. Heyd, Charles G.: "Liver Deaths" in *Surgery of the Gallbladder*, J.A. M. A. **97**:1847 (Dec. 19) 1931.

9. Mason, E. C.; Davidson, E. C.; Matthews, C. W., and Rastello, P. B.: *A Study of Tissue Autolysis in Vivo*, J. Lab. & Clin. Med. **10**:622 (May) 1925.

10. Helwig, F. C., and Schutz, C. B.: *A Liver-Kidney Syndrome*, Surg., Gynec. & Obst. **53**:570 (Nov.) 1932.

hyperpyrexia and coma. Also, in the differential diagnosis, one must include the possibility of uremia, certain types of intracranial lesions and severe peritonitis. However, in each of these conditions characteristic features can usually be recognized.

Because of the rapid course of postoperative gas bacillus infection, early recognition is essential if any result is to be expected from treatment. At best, treatment of this distressing complication is disappointingly ineffective. Measures directed at lowering the temperature, combating the toxemia and supporting the circulation are indicated. Specific antitoxin should be given. Intravenous and subcutaneous infusions of large quantities of saline and dextrose solutions may be used in an attempt to offset the shock and toxemia. Concentrated solutions of dextrose are indicated because of the extensive damage to the liver and because of the need for a diuretic. There may also be some virtue in a 50 per cent solution of dextrose as an antipyretic agent. At the first suspicion of the presence of this complication, large doses of gas bacillus antitoxin should immediately be administered intravenously. The usual skin test for sensitivity should be performed. From one to four therapeutic doses of polyvalent antitoxin containing at least 10,000 units each of *B. Welchii* and *vibrio septique* antitoxin per dose should serve as the initial administration. An additional therapeutic dose should be given intramuscularly. The intravenous administration of antitoxin should be repeated every two to four hours during the crucial period. If crepitation is elicited in the wound, the sutures should be removed, the wound laid open and smears of the exudate taken. Free incisions may be necessary if the process is extensive. Hydrogen dioxide or surgical solution of chlorinated soda may be instilled into the wound at frequent intervals through Carrel-Dakin tubes.

When the infection involves the blood stream, peritoneum or liver, the outlook seems hopeless. The prognosis in cases of gas bacillus infection localized in the abdominal wall depends on the virulence of the particular bacterial strain, the severity of the toxemia and the resistance of the patient. The early institution of adequate treatment may be the deciding factor in the outcome. The mortality in any event will be discouragingly high. Death occurred in our 4 cases.

#### REPORT OF CASES

CASE 1.—M. S., a salesman, 40 years old, was admitted to the hospital on Oct. 19, 1932, complaining of loss of weight for one year. For fourteen months the patient had suffered intermittent attacks of acute epigastric pain followed by vomiting. There had been periods of constipation, with the passage of small black lumps after catharsis. His appetite became poor, and he became progressively weaker. He had lost 40 pounds (18.1 Kg.) during the previous twelve months.

Physical examination revealed a well developed, undernourished man, whose skin and mucous membranes were pale. The heart, lungs and abdomen were normal. The blood pressure was 110 systolic and 75 diastolic. Rectal examination gave negative results. The urine was normal. The blood count showed: red blood cells, 3,250,000; hemoglobin content, 50 per cent; white blood cells, 6,700, and the differential smear was negative. Stools showed occult blood on all examinations. The results of serologic tests were negative. Gastric analysis showed nothing remarkable. A barium sulphate enema showed a constant narrowing at the upper portion of the ascending colon, about 7 cm. in length, having the characteristic appearance of annular growth, probably carcinoma. Roentgenograms revealed no evidence of metastases.

On October 26, under nitrous oxide, oxygen and ether anesthesia, the cecum and ascending colon were resected, and an ileotransverse colostomy and enterostomy were made. The patient left the operating room in good condition. His temperature gradually rose, reaching 104.6 F. the day following operation. Simultaneously the pulse rate increased to 144, and the respiratory rate to 40. The abdomen was flat and soft. The enterostomy tube functioned well. The blood pressure gradually became lower. The total urinary excretion was only 3 ounces (84.9 Gm.). Dextrose and saline solutions were given without any effect. On the morning of October 28 the temperature was 110 F., the pulse rate 160 and the respiratory rate 40. The patient grew comatose and his blood pressure gradually became imperceptible. Stimulants were given, but to no avail. At 4 a.m. on October 28, the patient died. Two hours before death, examination of the abdomen revealed for the first time, crepitation about the enterostomy wound.

At postmortem examination, performed eight hours after death, subcutaneous crepitation could be felt over the right half of the abdominal wall. There was a foul serosanguineous discharge from the stab wound around the enterostomy tube. The muscles in this region were edematous, brown and crepitant. There was a small amount of turbid fluid in the peritoneal cavity. The spleen was soft, but of normal size. Gas bubbles could be expressed from its cut surface. The liver showed fatty degeneration. *Bacillus Welchii* was isolated from the abdominal wall. The suprarenal glands were necrotic. The presence of typical gas bubbles, surrounded by bacilli, was the prominent finding in the necrotic muscle of the abdominal wall.

*Comment.*—This case presented a fulminating toxemia from which the patient died thirty-six hours after operation. The ileostomy opening was undoubtedly the source of contamination with *B. Welchii*. The major features of the postoperative course were the hyperpyrexia and profound shock. The postmortem observations were typical.

CASE 2.—A. M., a man, 56 years old, was admitted on July 19, 1932, complaining of severe pain in the right upper quadrant of the abdomen of twelve hours' duration. There had been two similar attacks during the three years before admission with no history of jaundice, clay-colored stools, nausea or vomiting.

Physical examination revealed marked tenderness and spasm in the right upper quadrant of the abdomen and a tender mass the size of an orange in this region, just below the costal margin. The edge of the liver was palpable 3 inches (7.6 cm.) below the costal margin. The temperature was 100 F. (rectal) and the blood pressure was 145 systolic and 90 diastolic. The urine was normal; the blood count showed: white blood cells, 11,600; red blood cells, 3,150,000, and hemoglobin content 70 per cent. The stools contained bile. The icteric index



was 12.5, the nonprotein nitrogen, 32, and the blood sugar, 95. The results of serologic tests were negative.

On July 21, cholecystectomy with drainage was performed under spinal anesthesia. Twenty hours after operation the temperature began to rise, and examination showed some abdominal distention. The patient became drowsy. The urinary output was 4 ounces (9.32 Gm.) in the twenty-four hours following operation, in spite of a fluid intake of 4,000 cc. Thirty hours after operation the patient became comatose, and showed an icteric tint. There was twitching of the muscles about the mouth. Three more ounces of urine was obtained by catheterization. The temperature gradually rose to 110 F. and persisted at this level. The icteric index increased rapidly, and the skin became cold and clammy. The blood pressure fell steadily, and there was an increasing weakness of the pulse. The nonprotein nitrogen was 110 mg. and the blood urea nitrogen, 46. Death occurred forty hours after operation. Postmortem examination revealed early purulent peritonitis. The liver showed extensive degeneration, and was markedly enlarged. On sectioning it gas bubbles were noted. Bacilli Welchii were recovered from its cut surface. The spleen and suprarenal glands showed marked necrosis. An acute toxic nephritis was present. The brain was swollen, and on sectioning, after fixation, showed a "Swiss cheese" appearance. Microscopically the organs showed parenchymatous degeneration associated with gas bubbles and bacilli.

*Comment.*—It is significant that the clinical diagnosis was hepaticorenal insufficiency. This is not surprising in view of the presence of hyperpyrexia, coma, urinary suppression, jaundice and evidence of nitrogenous retention. This case illustrates the similarity between gas bacillus toxemia and septicemia and hepaticorenal insufficiency, and suggests that the element of hepaticorenal insufficiency is actually present in severe gas bacillus toxemia.

CASE 3.—C. D., a woman, 67 years old, was admitted on Jan. 19, 1933, complaining of recurrent attacks of sharp pain in the right upper quadrant and in the epigastrium during nine months before admission. One month before admission she had a severe attack associated with chills and fever. Three weeks before entry she noticed jaundice, which became progressively deeper. Following the onset of the jaundice the urine became dark and the stools clay-colored. The patient gave a history of a loss of 10 pounds (4.5 Kg.) during the month before admission.

Physical examination revealed marked jaundice; the temperature was 100.2 F.; the blood pressure was 150 systolic and 70 diastolic; the abdomen was prominent; the edge of the liver, somewhat tender, could be felt about one handbreadth below the costal margin. The urine contained: albumin, a slight trace; bile, 4 plus. Repeated examinations of stools revealed no bile. The red blood cell count was 4,100,000; the hemoglobin content 60 per cent; the white blood cell count, 7,500, the differential smear, normal; nonprotein nitrogen, 24 mg.; the bleeding and clotting time normal, and icteric index, 150.

The patient was prepared for operation with intravenous injection of solutions of dextrose and calcium chloride. On January 25, under spinal anesthesia, the abdomen was explored. The gallbladder was dilated, and the head of the pancreas was definitely thickened. Cholecystogastrostomy was performed.

Twelve hours after operation the temperature rose to 104 F. and the pulse rate to 140. Catheterization at this time yielded 2 ounces (58.6 Gm.) of urine. Eighteen hours postoperatively the temperature was 106 F., the pulse became almost imperceptible, and the blood pressure dropped to 75 systolic and 40 diastolic. The patient rallied slightly after an intravenous infusion of 500 cc. of a 10 per

cent solution of dextrose. Examination of the wound revealed no evidence of crepitation, but the abdomen was tense in its upper half, and there was more tenderness present than was expected. Twenty-four hours after operation the patient was in a comatose state; at this time she was completely anuric. The nonprotein nitrogen was 45 mg. Despite the administration of large amounts of fluids by clyses and concentrated dextrose intravenously, the patient failed to excrete any urine. Thirty-six hours postoperatively the temperature rose to 102 F., the pulse was not perceptible and the patient died in spite of all treatment.

At postmortem examination extensive parenchymatous degeneration of the liver, kidneys and suprarenal glands was found. The liver, on section, was seen to contain numerous gas bubbles, and *B. Welchii* was isolated from its cut surface. The pancreas showed chronic inflammation.

*Comment.*—The profound toxemia and rapidly fatal termination illustrate the typical manifestations of gas bacillus infection.

CASE 4.—E. E., a woman, 37 years old, a kitchen worker was admitted on April 14, 1930, complaining of diarrhea, headache and abdominal pain. For six days previous to admission there had been from ten to twelve watery brown stools each day. Three days before admission the patient had chills, fever, general malaise and sweats. There was generalized pain in the lower part of the abdomen.

The physical examination revealed: evidence of consolidation at the base of the left lung, and the abdomen, markedly protuberant, contained a large fluctuant tumor. The temperature was 104 F. (rectal); the pulse rate 110; the respiratory rate 25; white blood cells 22,000, and the urine normal. While under observation the temperature continued to be elevated, up to 103 F., and there was persistent leukocytosis. The Widal test gave negative results. The stools decreased to two a day. Blood cultures were negative. Ten days after admission the patient complained of burning micturition. Examination revealed a large abdominal tumor completely filling the pelvis. This was very tender, and the uterus could not be felt. The diagnosis of ovarian cyst with possible malignant degeneration was suspected.

On May 15, under spinal anesthesia, laparotomy was performed. Two large tubo-ovarian masses, the size of footballs, filled the abdomen. The left was larger than the right, and both masses seemed to contain foul, purulent material. The abscesses were broken into and the masses were removed with considerable difficulty. During the operation, a small opening was inadvertently made in the sigmoid flexure; this was immediately sutured. The patient was given an intravenous infusion of dextrose immediately following operation, and was returned to the ward. Late in the afternoon she showed evidence of shock; treatment by fluids administered intravenously and transfusion did not improve the condition, and the blood pressure continued to fall. The temperature rose to 107 F. and the pulse to 160. Despite this pyrexia, the skin was cold, moist and clammy. The patient lapsed into a coma, her respirations became irregular, and she died sixteen hours after operation.

The postmortem examination disclosed widespread peritonitis with walled-off pockets of foul-smelling pus. There were hemorrhagic pleuritis and pericarditis. Throughout the myocardium were small gas bubbles. The spleen was enlarged, congested and crepitant. The liver presented a typical foamy appearance. Microscopic sections revealed a widespread distribution of gas bubbles. At the periphery of the bubbles were numerous bacilli. Bacilli *Welchii* were cultured from the

heart, spleen and lungs. Extensive parenchymatous degeneration was present in the liver and kidneys. The suprarenal glands were almost completely necrotic.

*Comment.*—This case presents the picture of overwhelming toxemia and septicemia, from which the patient died within sixteen hours of operation. The accidental opening of the intestine was probably the mode of entrance of the bacteria. The major feature of the postoperative course was the hyperpyrexia associated with the clinical evidence of surgical shock.

#### SUMMARY

Gas bacillus infection as a complication of laparotomy is discussed and the factors responsible for its inception and development are presented.

The pathologic process is briefly described. There is extensive parenchymatous degeneration in the various organs with or without an associated infiltration by gas and bacilli.

The clinical picture is one in which an overwhelming toxemia brings death, usually within thirty-six hours after operation. An extraordinary hyperpyrexia occurs associated with hypotension, cold clammy skin and coma. These features should suggest the diagnosis. Crepitation may be present when the abdominal wall is involved. There is evidence of suppression of hepatic and renal function simulating certain types of so-called hepaticorenal insufficiency occurring after operation.

The treatment consists of measures directed at lowering the temperature, combating the toxemia and supporting the circulation. Anti-toxin should be administered immediately. The prognosis is extremely grave.

# THE BREAST

## I. LESION IN RABBITS RESEMBLING CHRONIC CYSTIC MASTITIS

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In the course of detailed studies of the histologic changes in the mammary gland of the rabbit during the growth and sexual cycles certain changes similar to chronic cystic mastitis in man were noted. The entire study will be offered for publication in a special journal. The observations here reported are, however, of sufficient general interest to deserve a wider audience.

Schill<sup>1</sup> in the course of a somewhat similar study incidentally mentioned somewhat similar observations. No pathologic interpretation was made.

During the present studies it was found that in the resting stages (i. e., the male breast, the virgin female breast and the resting post-lactation breast) the rabbit's breast presents a histologic picture which is in substance identical with the pathologic picture known in the human breast as chronic cystic mastitis. The elements of this picture are: cyst formation, epithelial hyperplasia and metaplasia, mixed cell infiltration, erosion of the epithelium and scarring of the stroma. One or more of these lesions occurs in more than 90 per cent of resting breasts.

Cyst formation is the most outstanding pathologic feature observed in these studies (figs. 1, 2 and 3). All grades of cyst formation are found, ranging from mild dilatation of the ducts to macroscopic cysts. These are practically always lined by pathologic epithelium. Usually the epithelial lining is metaplastic (figs. 1 and 3). There are also areas of hyperplasia (figs. 1 and 3) in the walls of these cysts. They frequently contain desquamated epithelium. Hyperplasia is manifest by simple increase in the number of epithelial cells (figs. 1 and 2) and by tufting of the duct lining (figs. 3 and 4). Simple hyperplasia is probably the most constant pathologic element present. Metaplasia (figs. 1 and 3) varies in degree from flattening of the epithelium to an extreme attenuation of the cells. Mixed cell infiltration is most noticeable in the stroma underlying the pathologic epithelium (figs. 3 and 4). The

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This article includes a small portion of the work presented in candidacy for the degree of Master of Science, June 1932, University of Virginia.

1. Schill, L.: *Recherches sur la glande mammaire, sur les phases qu'elle présente au cours de son évolution et leur déterminisme*, Thèse de Lyon, 1912.

cells are of the wandering types. Erosion of the epithelium (fig. 2) is not so frequent as the aforementioned elements. The stroma beneath the eroded epithelium sometimes shows proliferation of connective tissue to the extent of scarring (fig. 2).

These changes occur in the male breast in the young and old alike. The virgin female breast presents a similar picture until estrus, when all these changes are erased and the breast assumes an orderly

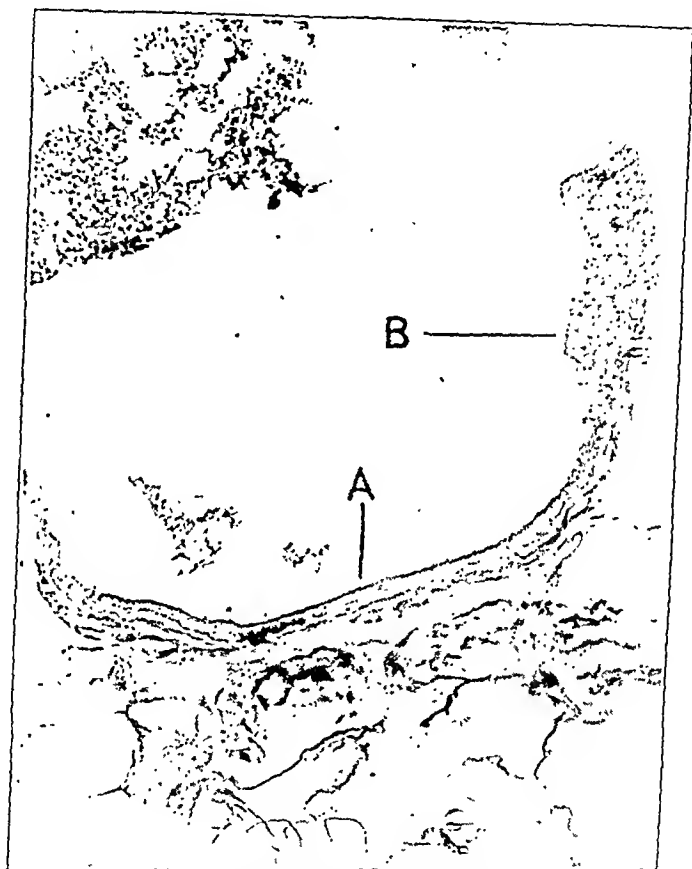


Fig. 1.—Section of male breast showing a part of a large cyst. There is metaplastic epithelium in the wall (*A*) with one area of hyperplasia (*B*). The surrounding stroma is adipose. Hematoxylin and eosin stain;  $\times 335$ .

morphology. In the multiparous female breast similar pathologic changes are found in the resting postlactation period, but as a rule these changes are not present in any stage of functional activity, i. e., in estrus, pregnancy, pseudopregnancy or lactation. In a few instances slight pathologic changes persist throughout the period of functional activity; in such cases they are never intensified by the hormone stimulation of the breast and they are seen only in the large ducts that are present from the earliest development of the gland. In general, the

more intense the hormone stimulation of the breast, the greater is the regularity of growth and the fewer are the pathologic elements.

The histopathology of chronic cystic mastitis includes just the changes described in the breasts of rabbits, namely, epithelial hyperplasia, formation of cysts, cellular infiltration and proliferation of connective tissue. The present observations are interesting from two points of view. In the first place, to judge by a fairly complete survey of

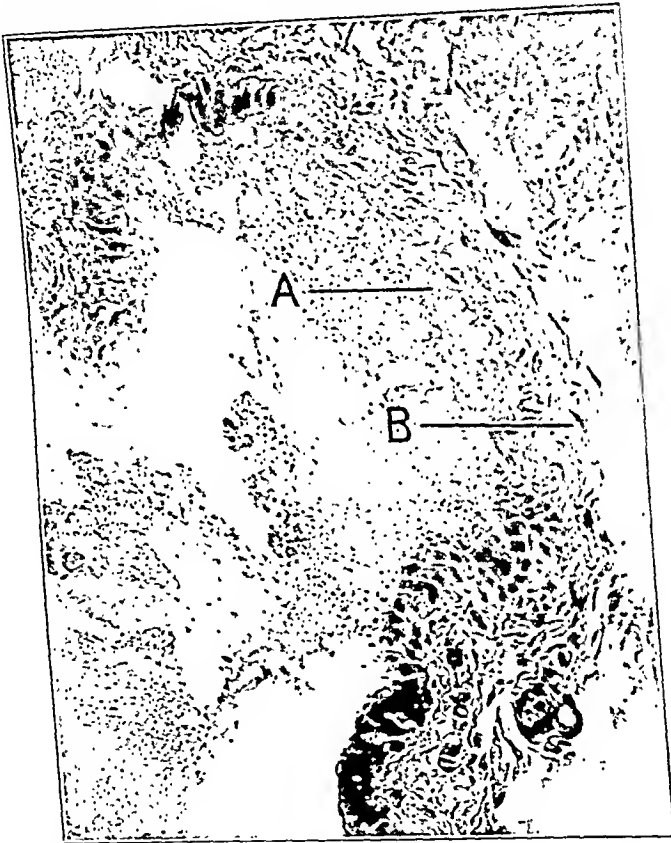


Fig. 2.—Section of male breast showing a part of a cyst with erosion of the epithelium at *A* and with scar tissue beneath. Young fibroblasts (*B*) are seen in the scar. The epithelium on each side of the erosion is hyperplastic. Hematoxylin and eosin stain;  $\times 335$ .

the literature, with the exception of Schill's observations, no change resembling chronic cystic mastitis has been observed in the rabbit.

In the second place, the relationship between hormone activity and the histologic picture in these breasts is exactly the reverse of the relationship between hormone activity and the clinical picture of chronic cystic mastitis. In the former instance estrus erases the pathologic elements; in the latter instance the premenstrual period of the menstrual cycle intensifies the clinical picture.

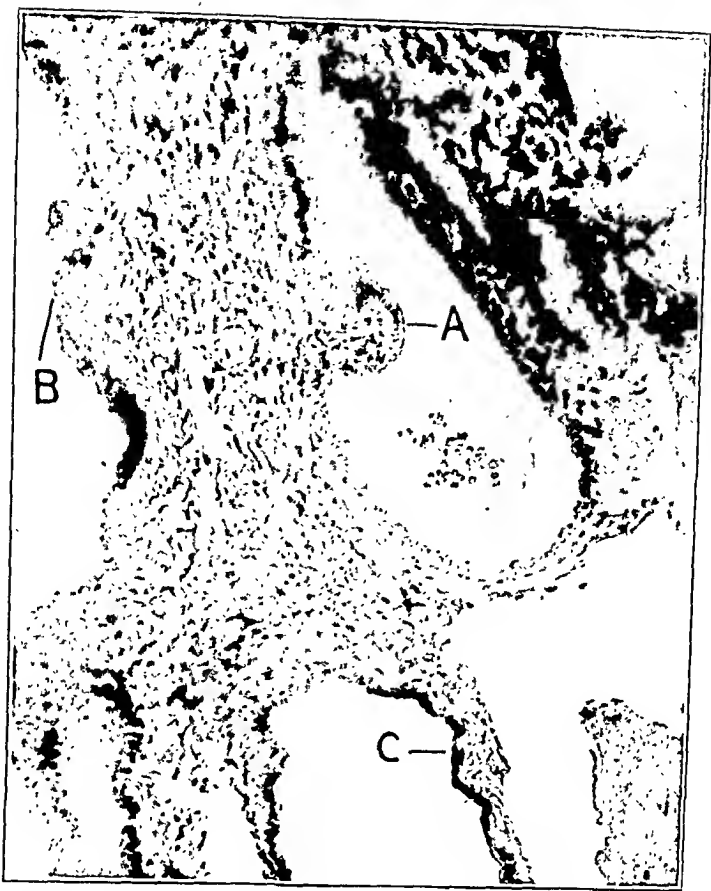


Fig. 3.—Section of male breast showing a part of four cystic ducts. One cyst contains a papillary projection (*A*) and a number of desquamated epithelial cells with a few wandering cells. One cyst shows hyperplasia (*B*) and another shows metaplasia (*C*). There is a mixed cell infiltration in the stroma. Hematoxylin and eosin stain;  $\times 167.5$ .

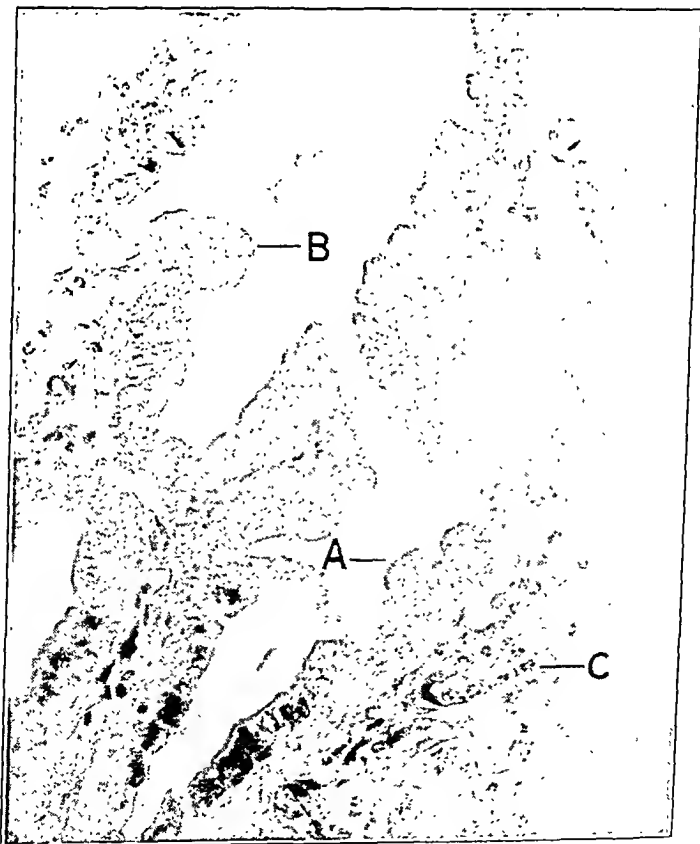


Fig. 4.—Section of male breast showing parts of two ducts with tufting (*A*) and papillary projection (*B*). There is a marked cellular infiltration in the stroma (*C*). Hematoxylin and eosin stain;  $\times 335$ .

These curious observations do not help to throw light on the etiology of chronic cystic mastitis. They suggest that there is a growth tendency on the part of the epithelial cells which need a hormone for regular orderly development and that when the hormone is absent the cells, subjected to this tendency to develop, do so irregularly. Under this conception the changes in the stroma may be secondary to the epithelial changes.



# PRIMARY LIPOSARCOMA OF BONE

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Malignant tumors which arise from preexisting lipoma and exhibit pronounced fatty elements have been described not infrequently since the original articles of Virchow<sup>1</sup> in the middle of the last century. The contributions of Robertson,<sup>2</sup> in 1916, and that of Seids and McGinnis,<sup>3</sup> in 1926, summarize the present knowledge of these tumors. It is noteworthy that these reports are concerned only with those tumors which were found perirenally or in the fascial planes of the extremities.

So far as a reasonable search of the literature will disclose, the only instances of primary liposarcoma of bone seen were the three cases reported by Stewart<sup>4</sup> from the Memorial Hospital, New York, in 1931. Stewart concluded from circumstantial data that his tumors were primary in the bone, and stated "we are not in a position of absolute certainty in stating this." Again, he said: "The only constituent of bone or bone marrow unrepresented in the tumor field seems to be the fat tissue."

There were also a few cases of benign lipoma which were apparently of periosteal origin (Bartlett<sup>5</sup> and Geschickter and Copeland<sup>6</sup>) which in themselves may have been the site of malignant degeneration.

I now present the report of a case which, from the clinical and pathologic study, strongly suggests a periosteal origin of a liposarcoma.

## REPORT OF A CASE

*History.*—L. K. was admitted to the Highland Hospital on Jan. 1, 1932, with the complaint of pain in the left shoulder of four months' duration. The patient was a white, married, American housewife, 30 years of age. During the past fifteen years she had dislocated her left shoulder many times, but aside from a short period of discomfort following this she had had no trouble with the shoulder until four months previous to admission, when she first noted a light aching pain similar to that following dislocation. This had persisted and had

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From the East Orthopedic Service, Highland Hospital; Dr. N. Austin Cary, Chief.

1. Virchow: *Virchows Arch. f. path. Anat.* **4**:468, 1854; **11**:281, 1857; **32**:545, 1865.

2. Robertson, H. E.: *J. M. Research* **35**:131, 1916-1917.

3. Seids and McGinnis: *Surg., Gynec. & Obst.* **44**:232, 1927.

4. Stewart: *Am. J. Path.* **7**:87, 1931.

5. Bartlett: *Periosteal Lipoma*, *Arch. Surg.* **21**:1015 (Dec.) 1930.

6. Geschickter, C. F., and Copeland, M. M.: *Tumors of Bone*, New York, Am. J. Cancer, 1931, p. 605.

become progressively more severe. She consulted a physician concerning it, who told her that it was "rheumatism" and treated her. During the previous month the pain had become more severe, and coincident with this there began a gradually increasing swelling in the axillary area.

Since the onset there had been a slight fever off and on. She located the pain at the tip of the shoulder. It was made worse by movement, especially anterior flexion and abduction of the arm at the shoulder.

Aside from the aforementioned recurrent dislocations of the shoulder, she had had a heart murmur since the age of 6 and occasional head colds. She had been married 11 years, and had two children, one living and well and the other dead. Her menses were normal, and there was no memory of serious previous illness. The family history revealed no familial or malignant disease.

*Physical Examination.*—The patient was a poorly nourished, thin white woman lying quietly in bed in no apparent distress. The heart was enlarged to the left with a systolic murmur at the mitral area. The blood pressure was 110 systolic and 55 diastolic; the temperature, 98.4 F.; the pulse rate, 75, and the respiratory rate, 18.

On the upper part of the left extremity was a symmetrical, rounded swelling over the head and trochanter of the humerus. It was not inflamed, and the vessels overlying it were not engorged abnormally. It was cold, smooth and homogeneous on palpation. There was an increase in tension and elasticity suggesting fluid under pressure. The mass lay beneath the deltoid muscle, which was freely movable. The mass was not movable and lacked the feel of an encapsulated tumor. The arm through the proximal end measured 2 inches (5.08 cm.) greater in circumference than the normal right arm. There was only slight tenderness on pressure, but passive forward elevation of the shoulder produced pain.

*Laboratory Examination.*—The Wassermann reaction of the blood was negative. The blood showed: hemoglobin concentration, 72 per cent; white blood cells, 6,400 per cubic millimeter; polymorphonuclears, 49 per cent; small lymphocytes, 40 per cent, and 11 per cent large lymphocytes. The urine was normal.

*Roentgen Examination.*—A roentgenogram made on Dec. 31, 1931, of the anteroposterior view of the left shoulder was reported by Dr. C. M. Pearce as showing a rarefaction in the greater tuberosity and upper 2 cm. of the humerus, with a bulging of the cortex over the tuberosity. Neither perforation nor formation of new bone was visible. The marked rarefaction and bulging of the greater tuberosity were suggestive of early formation of bone tumor, but the diffuse mottling in the upper portion of the shaft argued rather for early osteomyelitis.

Examination made on Jan. 6, 1932, in anteroposterior stereoscopic views of the shoulder (fig. 1), reported by Dr. W. H. Sargent, showed a destructive process in the greater tuberosity of the humerus, evident in a small rather well defined area about 1 cm. in diameter lying close to the cortex. There was a slight mottling of the bone adjacent to this area, and extending down into the shaft about 2 inches. There was no evidence of rupture through the cortex as yet. In the area of swelling of the soft tissue was a faint shadow lying adjacent to the shaft which suggested periosteal reaction. Conclusions in this case were impossible without the clinical findings. If the patient had had fever and other findings to coordinate it, I should have been inclined to consider the condition as due to infection. Its diffuseness was rather against new growth.

There was no evidence of a pathologic process in the lungs. The cardiac shadow was globular and there was considerable fulness in the auricular area.



Fig. 1.—Anteroposterior roentgenogram of the left shoulder on entry to the hospital. Note the destructive area in the greater tuberosity of the humerus and the mottling of the bone adjacent to this area. In the soft tissues the bulging mass beneath the deltoid muscle can be seen.



Fig. 2.—Photograph of the arm involved with tumor. Note the extreme swelling of the upper part of the arm. The biopsy wound is open, with the tumor extruding.

*Course.*—A diagnosis was not clear, so further attempts were made to arrive at one. On January 8, an aspiration was done, in the belief that a lesion such as bursitis, osteomyelitis or ganglion could be ruled out this way. This would not be considered good surgical practice, and I feel that in this case it served to stimulate the growth of the tumor. Only a small quantity of bloody material was obtained, which microscopically showed normal blood.

By January 20 (fig. 2) the pain and swelling in the arm had increased considerably, and a specimen of tissue was removed surgically for biopsy. The deltoid muscle was opened by blunt dissection. Immediately on entering the subdeltoid area a large amount of slimy jelly-like material filled the wound. It was grayish-yellow and very friable, with stringiness. A large amount was scraped out from beneath the deltoid muscle, to which it showed no attachment. There was no capsule. The only point of attachment was to the tuberosity of the humerus. The bone at this point was definitely infiltrated with the tumor, and was easily perforated with a blunt hemostat. The involvement of bone extended down the neck from 2 to 3 cm. The tumor had a free blood supply which necessitated packing to control hemorrhage at frequent intervals. Specimens of the bone and tumor tissue were removed and examined by Dr. G. Moore, who reported as follows: The most striking characteristics from a microscopic standpoint were the remarkable variations in the size and shape of the cells and the number of bizarre nuclear forms. Individual cells varied from small round or spindle cells to enormous giant cells of both mononuclear and multinuclear forms. In the larger cells the outlines were indistinct, and there was a curious multiplicity of pattern. The cytoplasm showed many vacuoles which, on frozen section, stained with sudan III, were found to contain fat droplets. The nuclei were likewise peculiarly diversified, and showed a moderate number of mitotic figures. Tumor cells dominated the picture, with little evidence of supporting fibrous tissue. The blood supply was free, and there were many hemorrhagic areas. The picture was that of a malignant mesoblastic tumor, which, because of its lipid content, might well be placed in the group of the liposarcomas.

With a proved diagnosis, roentgen therapy was instituted by Dr. W. H. Sargent, it being known that many reported liposarcomas are radiosensitive. Numerous transfusions of citrated blood were also undertaken. When a checkup roentgenogram of the chest failed to show any metastases, a radical shoulder girdle amputation was decided on. This was done on February 23. The patient withstood the surgical procedure satisfactorily, but died six hours later of delayed shock.

*Autopsy.*—A complete autopsy was performed by Dr. George Calvin, who reported as follows: The general external examination revealed a normal condition except for the absence of the left arm at the shoulder girdle, apparently amputated recently. The right lung showed heavy adhesive pleuritis throughout the entire lower lobe. There was no free fluid. The cut sections were normal except for scattered small, soft, metastatic nodules. Sections of the nodules in the lung showed them to be composed in large part of the same cells containing lipid found in the primary tumor of the arm. The heart showed adhesive pericarditis, and the mitral valve sclerosis and retractions. The liver, spleen and kidneys revealed no metastases and except for congestive change were normal.

The amputated arm was examined immediately postoperatively, and frozen sections were stained with fat stains. These showed the previously reported pathologic process, but served to demonstrate the marked preponderance of fatty elements in the tumor.



Fig. 3.—Photomicrograph of the tumor showing the involvement of bone. The vacuolated areas, when freshly stained with sudan III, were shown to be filled with fat;  $\times 200$ .

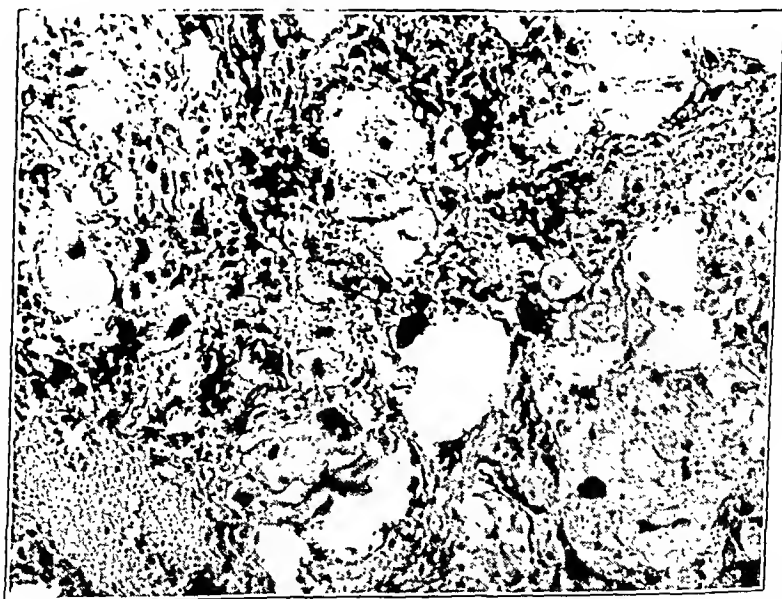


Fig. 4.—Photomicrograph of section of the tumor tissue showing various-sized cells and diversified nuclei;  $\times 500$ .

## COMMENT

It is well known that fatty tumors termed "lipoma" may undergo sarcomatous change, and the first impression was that this was such a tumor. There were, however, several factors which did not coincide with this point of view. First, the tumors that have been reported, few of which involved the upper extremity, did not involve the bone, but arose in the fascial planes from a preexisting lipoma which was always encapsulated, and the history of its presence preceded for long periods its malignant change. Only one instance of involvement of bone was noted by Stewart, that of Neinhuis, in which case the process was considered metastatic.

The clinical picture in this case was more characteristic of so-called periosteal sarcomas, but the pathologic findings did not fit this classification. That this was not a benign periosteal lipoma which had undergone sarcomatous change would seem evident from the lack of encapsulation and the absence of tumor prior to the onset of severe symptoms.

The osseous involvement was apparent in the earliest roentgenogram, and at the time of biopsy there was no infiltration of the subdeltoid sheath, which would have been a much more logical site for local metastases or invasion than the cortical bone if the tumor had arisen extra-periosteally.

The histologic picture of the tumor both locally and in the myriad of small metastases in the lungs, which were not demonstrable by x-ray film, strongly suggests that this was a tumor of fatty origin. The influence of the trauma from repeated dislocations of the shoulder is of definite interest and must be assumed to have been a factor in the origin or spread of this new growth. It may be well in the future to stain more of the frozen sections of biopsy specimens with some standard fat stain to establish more accurately the frequency of these malignant processes.

## SUMMARY

The general subject of malignant fatty tumors involving bone is considered, and a case reported which, from the clinical and pathologic evidence, strongly suggests its origin from the fatty elements of bone. It is hoped that more frequent use of fat stains at biopsy will disclose more facts in this obscure tumor field.

# CHANGES IN THE BONES OF EXTREMITIES AMPUTATED BECAUSE OF ARTERIOVASCULAR DISEASE

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AND

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Histopathologic descriptions of bones of extremities amputated because of gangrene, contingent on vascular occlusion, are practically nonexistent. In caring for patients in whom gangrene of the extremities is developing, it is often the practice, in the course of clinical observation, to make roentgenographic records of the diseased parts. The records are generally taken with a view to ascertaining the extent, severity and character of the changes in the soft tissues and, more particularly, of those in the bones. But the sparsity of pathologic studies of bones of gangrenous extremities necessarily limits the intelligent roentgenographic interpretation of any changes that may exist.

The presence of extensive roentgenographic changes in all of the bones of the right lower extremity of a patient for whom a diagnosis of thrombus in the right common iliac artery, probably extending into the aorta, was made, gave stimulus to our study (fig. 1). By this work we hoped to clarify the subject of histopathologic changes occurring in the bones of surgically amputated extremities with vascular occlusion and resultant partial gangrene. One of our special objects was to coordinate particular histologic changes with corresponding roentgenographic abnormalities, thus providing a factual basis for roentgenographic interpretation. Eight specimens were studied; in most instances an opportunity was afforded for the gross and histologic investigation of the femur, tibia and the tarsal, metatarsal and phalangeal bones. We were particularly interested in ascertaining the condition of the bones high above the level of gangrene and infection. In evaluating the gross, roentgenographic and histologic changes, the necessity of due regard for the rôle played by infection, inactivity and the so-called trophoneurotic influences was borne in mind.

Mueller<sup>1</sup> seems to be the only person who has previously undertaken an inquiry of this nature; he examined the bones from four lower extremities, amputated because gangrene of as many as from two to three toes had proceeded from arteriosclerosis and vascular occlusion

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1. Mueller, W.: Beitr. z. klin. Chir. 138:614, 1926.

(the nongangrenous portion of the extremities likewise showed evidences of circulatory failure). In the interstitial lamellae of the cortical bone at some distance above the site of general tissue necrosis (even as high as in the tibia), he found and stressed the prominence of widespread empty bone cell lacunae. The bone cells of the haversian lamellae as well as those of the ground lamellae (especially the inner lamellae) and the spongy trabeculae stained well and were not degenerated. Mueller considered necrosis or death of the bone cells of the cortical interstitial lamellae (or others at a distance from the haversian canals) to be the direct effect of disturbance and diminution of the circulation and concluded that this demonstrated a differential reaction of the bone cells to partially diminished circulation, the cells of the interstitial lamellae of compact bone being particularly sensitive in that respect. The unfavorable anatomic position of the cells was considered responsible for their greater susceptibility. Furthermore, Mueller reported that the myeloid and connective tissue elements of the marrow were in all four instances well preserved, and that they showed no evidences of osteogenic activity, nor were regenerative phenomena apparent to any degree in the bones.

For the purpose of control, Mueller examined a number of corresponding bones from older persons without gangrene, who ranged in age from 70 to 89 years. In these subjects absence of nuclear staining of the interstitial lamellae of compact bone could also be observed, but it was never of such regularity or extent as that which developed in the arteriosclerotic patients with gangrene; the degree was on the whole proportional to the age. Likewise, no regenerative phenomena were found in the bone or the marrow of these specimens. In the control, nongangrenous extremities, extensive changes in the bone, he believed, could be related to the existence of arteriosclerosis.

#### INTERSTITIAL LAMELLAE IN THE COMPACTA OF OUR CONTROLS

There is no doubt that Mueller was correct in emphasizing that the cells of the cortical interstitial lamellae in his amputated specimens had a greater susceptibility and tendency to die. This predisposition exists even in normal bone, despite the lack of attention focused on it by histologists generally. The nature, the mode of formation and the position of the interstitial lamellae of normal compact bone bespeak the unmistakable inherent disposition favoring such susceptibility. Our own histologic studies of bone have indubitably indicated this predilection: Interstitial lamellae are fragments of old and splintered haversian systems; in the disintegration of these systems, interstitial lamellae form an important supporting mass for newer haversian systems and as a result become disadvantageously placed for the receipt of nutrition. This is not the fate of the cells of the interstitial lamellae of compact



bone alone; wherever bone cells are disadvantageously situated for the reception of nutrition, they tend to die. A simple example of this tendency is the condition of the deeply placed cells in a compact and sclerosing calvarium; here the deeply embedded cells between obliterated or obliterating diploe evidence the greatest absence of staining. A slight degree of degeneration and death of the cells of deeply placed lamellae of compact bone are normal manifestations even in young adults; with increasing age the degree and extent become progressive, provided the bone always remains compact. This gives no abnormal appearance roentgenographically.

The foregoing assertions are based on a study of numerous sections of bone observed in the course of routine examinations and specifically on the character of the changes seen in the femurs of six patients (ranging from 8 to 62 years of age) who died from various causes and whose extremities were not gangrenous. Cross-sections were taken through the middle of the femurs.<sup>2</sup>

CASE 1.—One of the six patients, a woman, aged 36, died of cardiac failure, associated with rheumatic endocarditis and terminal pulmonary infarction. The cross-section of the femur showed normal general architecture, the haversian canals being of the usual diameter. On the whole, the cells and the ground substance of the haversian systems stained well. An occasional haversian system with a plugged central vessel was observed, and naturally the nuclei and the ground substance of an osteon of this sort stained poorly. The interstitial lamellae throughout the section stained more poorly than the rest of the lamellae. In some of this interstitial bone all of the nuclei were absent from their lacunae; in other portions only a few poorly staining cells were to be seen, and in still other areas as many as half of the cells were in evidence. The inner and outer ground lamellae were for the most part as well preserved as the haversian lamellae, while the cells of the spongy trabeculae stained well; the marrow also showed nothing abnormal.

The foregoing description applied generally to several of the sections of the other femurs studied (fig. 2). There were variations dependent

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2. In studies of this nature, the utmost attention to technical details in the methods of preparing the sections is imperative. Otherwise, the appearance of artefacts, particularly in sections of compact bone, invalidates the usefulness of the examination. First, in preparing compact bone for histologic study, it is necessary to take thin segments from 2 to 3 mm. in thickness for fixation; next, these segments should be fixed promptly after removal from the body. For the best preservation of the cellular elements, we prefer a fixative containing bichromate (Helly's fluid); decalcification with 5 per cent nitric acid is then satisfactory; embedding must be in pyroxylin (celloidin) or the sections will be fragmented; careful staining with hematoxylin to the point of overstaining and proper decolorization and differentiation are also necessary. Emphasis on these details may seem elementary, but it is vitally important to observe these rules in obtaining reliable as well as good histologic sections. For further details, the reader is referred to other publications (Jaffe, H. L.: *Methods of Histologic Study of Normal and Diseased Bone*, Arch. Path. 8:817 [Nov.] 1929. Riemer, B.: *J. Techn. Methods* 13:72 [March] 1934).



Fig. 1.—A roentgenogram demonstrating the character of the lesions in some of the bones of the foot. General porosity is apparent; small, punctate areas of rarefaction are clearly seen; these are pronounced in the compacta of the metatarsal bones.

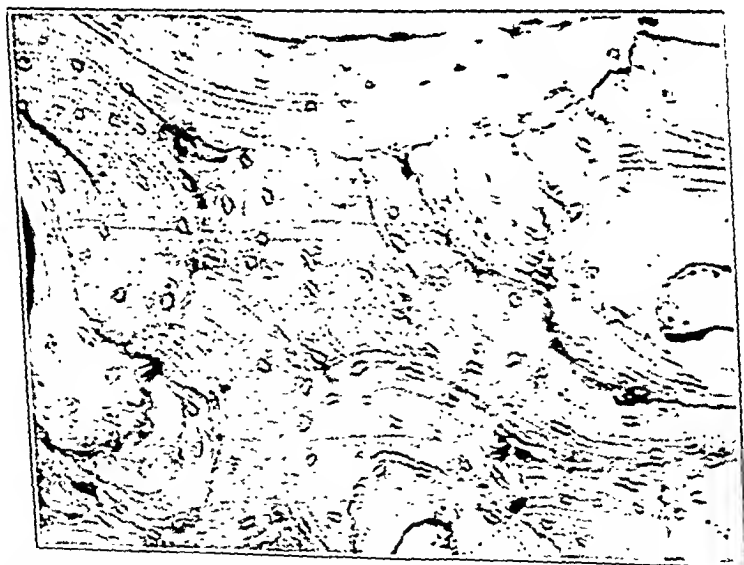


Fig. 2.—A small area from a femoral cortex, in cross-section. The patient was 36 years of age. Nuclei are absent from the interstitially placed bone; the nuclei of the osteons stained well;  $\times 300$ .

on the age of the patient, the nature of the illness, the character of the terminating disease and other features. Even in the femur of the 8 year old subject, the cortical interstitial lamellae showed a leaning in the same direction.

CASE 2.—In another patient, a woman, aged 44, who had progressively lost weight for about a year and who died of atrophic cirrhosis of the liver and its usual concomitants, the femoral section disclosed the presence of a moderate degree of simple osteoporosis. This was not sufficient to reduce the interstitially placed bone materially; therefore it showed fairly large areas with absence of nuclear staining.

CASE 3.—The femoral section of one patient who died shortly after admission to the hospital of infarction of the cardiac muscles due to coronary occlusion also presented a slight degree of osteoporosis. The patient had suffered from diabetes mellitus of moderate severity and showed at postmortem examination, in addition to other changes, extensive generalized arteriosclerosis; the femoral artery in the vicinity of the region from which the piece of femur had been removed evidenced definite thickening with medial sclerosis and early calcification. As in the other sections of bone, the cells of the interstitial lamellae stained most poorly, but, curiously enough, the changes were less advanced than those in the other cases; that death occurred rather quickly may account for this.

What conditions the greater susceptibility of the cells of the interstitial lamellae is unknown; whether its prevalence depends directly on the advent of arteriosclerosis in the extra-osseous blood vessels is a moot question. Whether disintegration and death of the cells of deeply placed lamellae of compact bone precede the inception of such changes as are produced by senile osteoporosis or whether they contribute to the induction of brittleness so often found in senile bones is still open to investigation.

#### BONES OF EXTREMITIES IN WHICH CHRONIC VASCULAR DISEASE LONG PRECEDED GANGRENE

In this laboratory during the past few years there has been a striking reduction in the number of extremities received that were amputated because of gangrene. This is only a reflection of the great improvement in the clinical care of patients with impending gangrene. Previously, its first appearance in the toe of a diabetic patient was usually the signal for high amputation to eliminate any possibility of progressive infection and diabetic coma; now, on the contrary, conservative measures often result in recession of the serious local changes. Often, too, patients with considerable organic vascular disease of the extremities may entirely escape amputation, although they have been in imminent danger of extensive gangrene. When such a patient finally has to undergo amputation, it is usually because the infection cannot be controlled, although treatment may have delayed the necessity for amputation for months. Thus, the long interval of time allows such factors as infec-

tion, inactivity and the so-called trophomenrotic influences, in addition to the circulatory disturbance, to assert themselves. In fact, the strong and natural tendency toward the development of collateral circulation frequently reduces to a place of second importance the effect which the vascular obstruction has on the changes in the bones.

These premises are borne out by the results of examination of the right lower extremity in the following case:

CASE 4.—A man, aged 68, had had his left lower extremity amputated four years previously because of gangrene of the toes. Difficulty with the right lower extremity began about two years before his last admission. At that time the right foot suddenly became cold and insensitive; he suffered from cramps in the foot and could not walk. Examination then revealed areas of anesthesia over the dorsal surface of the foot; a bluish discoloration at the tip of the large toe, in the vicinity of the toe-nail, appeared; finally this area was converted into a gangrenous bleb. With conservative treatment the patient's condition slowly improved, the local symptoms receding, so that he was able to leave the hospital. About a year later gangrene appeared in the toes, progressing slowly; during this time part of the foot sloughed off. Finally a fulminating infection necessitated readmission for amputation. For almost a year and a half the patient had been confined to bed.

The amputated specimen demonstrated considerable infection and sloughing of the foot; some parts of the tarsal bones were visible through the slough; the infection and ulceration extended a distance up the leg. When the soft tissues of the leg and ankle were dissected, necrotic muscles, tendons and fascial tissues were everywhere encountered. The popliteal artery was extremely atheromatous and calcified, as were the anterior and posterior tibial arteries.

All of the bones were greatly affected even grossly; the femoral cortex was thinned as a result of a pronounced eccentric atrophy that had considerably enlarged the marrow cavity; anteriorly the cortical reduction had proceeded to such an advanced degree as to leave a mere shell, plainly eroded on the inner surface; the vascular canals of the femoral cortex were visibly enlarged; the medullary cavity contained soft, almost liquid, fatty marrow and delicate bony trabeculae (fig. 3). The tibia also cut with great ease; the upper portion of the medullary cavity was likewise filled with soft, fatty marrow, while in the lower third the marrow contained a number of liquefaction cysts. There was edema of the periosteum, and subperiosteal osteophytic new formations were observed in its upper portion. The tibial cortex, although not greatly thinned, was much more porous than normal.

Both the astragalus and the calcaneus were atrophic to such a degree that they could be compressed between the fingers; they were the only tarsal bones which were complete and which retained their original shape and position. Within the astragalus there was a large triangular, wedge-shaped, whitish-yellow focus of bone which was definitely demarcated from the surrounding bone; this extended to beneath the articular cartilage and occupied a large area in its posterior extremity. There was a similar but smaller triangular focus of necrotic bone at the anterior extremity of the astragalus. Otherwise, this bone and the calcaneus showed extensive resorption of the spongy trabeculae; large portions were occupied by soft, fatty marrow. Grossly, these bones did not present evidence of osteomyelitis, although the surrounding soft tissues were extremely necrotic and partly hemorrhagic (fig. 4 A and B).

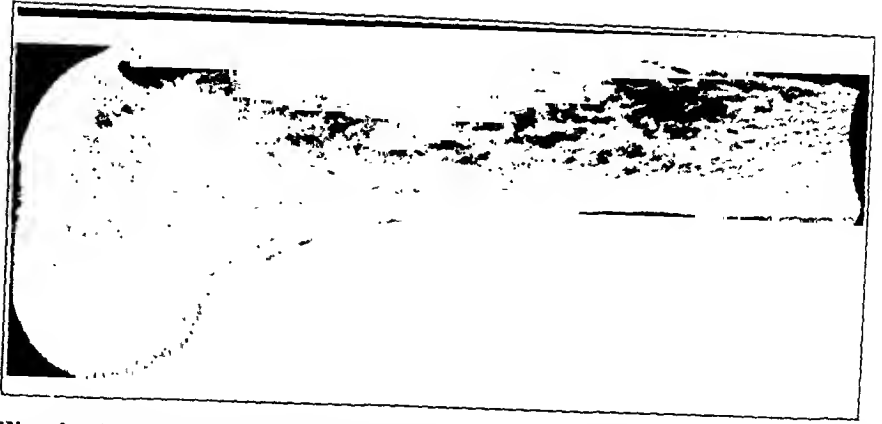


Fig. 3.—Roentgenogram of the sagittally sectioned femur. Extensive cortical thinning and rarefaction are evident, as also the enlargement of the medullary canal. For the histologic appearance see figure 5.



Fig. 4.—*A*, a triangular, wedge-shaped focus of necrotic bone in the posterior portion of the astragalus. The pronounced rarefaction of the rest of the astragalus and calcaneus is evident in this photograph, which is slightly reduced from normal size. *B*, roentgenographic appearance of the same necrotic focus in the astragalus, which casts a dense shadow (fig. 6).

Histologic study of the bones again pointed to the secondary importance of vascular disturbance; the changes in the bones were clearly much more dependent on the effects of infection and inactivity. A number of femoral cross-sections confirmed the gross appearance of rarefaction from the medullary side; the opened cortex contained congested and vascular myeloid marrow in its enlarged spaces. On the other hand, there was little cortical resorption from the periosteal side. Furthermore, the sections revealed that many of the haversian canals, particularly near the periosteal surface of the cortex, contained pink-staining plasma; the nuclei within such osteons showed partial or complete absence of staining. In addition, some of the nuclei of other haversian systems also demonstrated poor staining; in places the nuclei were entirely absent from their lacunae. The interstitially placed bone, however, most pronouncedly illustrated the absence of nuclei from their lacunae, but this bone was relatively slight in amount (fig. 5). A longitudinal section through one of the femoral condyles disclosed rather good staining of the nuclei of the spongy trabeculae and of the intertrabecular fat. Cross and longitudinal microscopic sections from the tibia showed, aside from the rarefaction due to eccentric atrophy, absence of nuclear staining from the interstitial bone as the principal feature.

The microscopic examination of the astragalus demonstrated the posterior, triangular, wedge-shaped, infarct-like area to be composed of thick, spongy trabeculae of dead bone; the marrow between the trabeculae had not been vascularized; this infarcted area was surrounded by vascular, fatty marrow, but none of its vessels had penetrated the necrotic marrow within the infarct area. The articular cartilage overlying the infarcted area was also necrotic (fig. 6). The portion of the astragalus that had become atrophic through disappearance of the trabeculae contained somewhat vascular and edematous fatty marrow; within this marrow a number of newly formed osseous trabeculae were to be seen, as well as a moderate amount of newly proliferated fibroblastic tissue. At the base of the bone, a large area of subchondral infection was to be found; no evidence of thrombosis of the nutrient vessels was discovered. The spongy trabeculae of the calcaneus were pronouncedly atrophic; the intertrabecular fatty marrow was edematous and showed engorged blood vessels. The nuclei of the atrophic trabeculae stained well. The fat and soft tissues about the bone were infected; the infection which extended along the achilles tendon invaded the bone and produced local areas of osteomyelitis. Thus in the astragalus and calcaneus much of the atrophy apparently was due to infection and inactivity, while the infarct-like lesions were to be attributed to occlusion of the vessels supplying these areas.

That arterial disease of long standing may exist when the bones do not show significant roentgenographic changes was brought out by a number of our specimens, one of which is described in the succeeding paragraphs.

CASE 5.—A woman, aged 59, was first admitted on Oct. 17, 1932, with a history of pain in the left large toe, of two weeks' duration. The pain was chiefly nocturnal. No dorsal pedis artery was palpated. After medical therapy had been carried out for two months, the patient was discharged. On Feb. 1, 1933, she was readmitted because of the sudden appearance of gangrene of the left large toe and an ascending inflammation of the proximal part of the foot. A blood culture on admission gave positive results. The patient died in spite of amputation of the leg.



Fig. 5.—An extremely rarefied and spongy femoral cortex; the enlarged spaces are filled with myeloid marrow; the resorption from the periosteal side is insignificant. The pronounced enlargement of vascular canals resulting in the formation of large spaces has reduced the cortical thickness to the degree observed in figure 3. The interstitially placed bone is relatively slight in amount;  $\times 30$ .

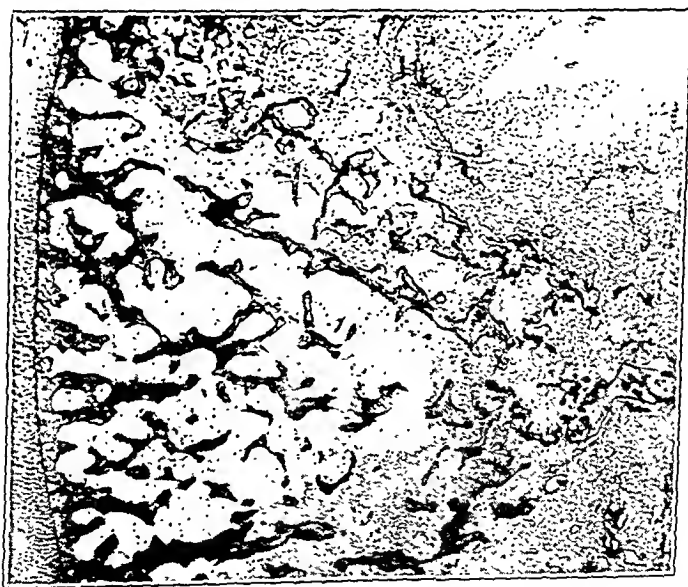


Fig. 6.—The thick but necrotic trabeculae of the triangular, wedge-shaped focus in the astragalus demonstrated by figure 4;  $\times 5$ .

The specimen showed the large toe discolored a reddish, purplish black as far as the metatarsal phalangeal joint; the second, third and fourth toes were also discolored, from reddish purple to black, especially on their ventral surfaces; the small toe showed no evidence of gangrene. Frank purulent infection was absent from the gangrenous toes; there was no perforating wound anywhere. The muscles of the leg were found to be reddish and fairly well preserved; when the incision was carried to the foot the tissues in the nongangrenous area showed nothing in particular except edema; in the gangrenous regions, the tissues were hemorrhagic and edematous. The anterior tibial, posterior tibial and dorsalis pedis arteries were



Fig. 7.—The roentgenogram of the foot of a woman, aged 59, in whom gangrene was impending for some months; amputation was performed because of gangrene of several toes, which appeared suddenly. Nothing striking is seen except the rarefaction of the terminal phalanx of the large toe. Compare this with figure 1.

found to be occluded by a thrombus. Roentgenograms of the specimen were taken, but none of the bones of the foot or leg showed anything striking in the film, although the terminal portions of the four toes were definitely gangrenous; at most there was only the slightest indication of atrophy of all of the bones. This, considering the age and previous disability, is comprehensible (fig. 7).

Microscopic sections of the tibia showed that most of the cortical interstitial lamellae stained poorly; some of its cells still stained fairly well; most of the



cells about the haversian lamellae stained well. Numerous sections from the other bones, furthermore, demonstrated that the more closely situated they were to the sites of impaired circulation, the greater was the nonstaining of the bone cells; always it was the deeply situated cells that were degenerated (fig. 8). The large toe, which showed massive gangrene of the soft tissues, demonstrated the greatest degree of devitalization of its bones.

Four other specimens from patients suffering from arteriosclerotic gangrene of a lower extremity, with or without attendant diabetes mellitus, resembled the two specimens detailed earlier. All six specimens illustrated again what has been repeatedly stressed: No matter how advanced the organic vascular disease may be, no matter how long since the inception of the vascular disturbance, no specific or characteristic

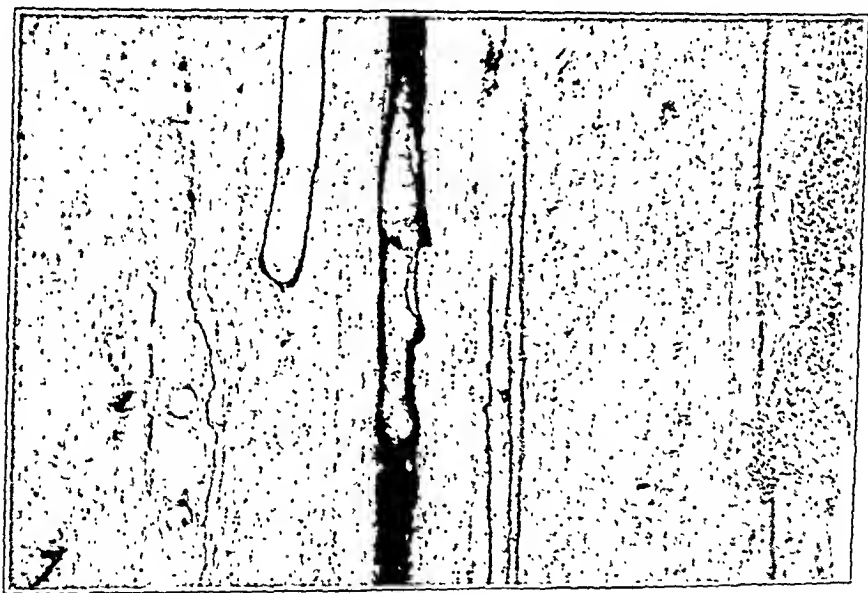


Fig. 8.—The cortex of the proximal phalanx of the second toe of the foot is shown in figure 7. Grossly, the bone was apparently normal. The soft tissues about the bone were not gangrenous. Microscopically, the cortex showed extensive areas of absence of nuclear staining. Roentgenographically this phalanx showed nothing unusual;  $\times 150$ .

changes in the bones are consistently demonstrable roentgenographically (this is in marked contrast to the well known changes produced in the terminal phalanges and evidenced roentgenographically by Raynaud's disease and scleroderma). This roentgenographic and histologic correlation demonstrated, furthermore, that unless the histologic processes were clearly understood, a strong possibility for misinterpretation of the roentgenograms exists. For instance, the bones of a gangrenous toe may appear roentgenographically normal, while histologically its phalanges may show an extensive, purulent infection of the medullary cavities; osteomyelitis, therefore, exists, but the roentgenologist is at

a loss to recognize it, as no periostitis is present. The periosteal reaction is naturally absent because of the devitalization of the soft tissues about the bone. Again, the roentgenographic appearance of a phalanx or a metatarsal bone may be within normal limits, or the roentgenographic shadows of such bone be even sharper than those of the adjoining ones: by contrast, the contiguous bones appear atrophic, but histologically these more clearly defined bones are likely to be completely necrotic.



Fig. 9.—Demonstrating part of the femur, tibia and fibula of a patient in whom an acute occlusion of the common iliac artery was followed a few months later by marked rarefaction of all of the bones of the extremity. Collateral circulation was adequate to prevent immediate gangrene, although it was not sufficient for normal nutrition. Figure 1 shows the roentgenographic changes in the bones of the foot of this patient. Figure 11 shows the character of the microscopic changes in the femur.

They are sharply outlined in comparison with their neighbors because they have undergone rapid necrosis, while the neighboring bones may still be viable, thereby allowing atrophy to supervene.

If a bone or part of a bone becomes rapidly devitalized and if circulatory adjustments are made so that blood is resupplied to the bone,

after a little time an active revascularization occurs; the portions of the bone which have not undergone a revivescence become resorbed and replaced by new bone. In this event, the later roentgenographic appearance will be that of a spotted, punctate rarefaction (figs. 1 and 9). These punctate shadows of increased permeability are the result of enlargement of previously existent vessel canals and cortical erosion, particularly from the periosteal side. In regard to the latter feature,



Fig. 10.—Roentgenogram of part of the foot of a man, aged 43, who suffered from thrombo-angiitis obliterans. On admission the foot was swollen, but the leg on that side was atrophic; the dorsalis pedis artery and the posterior tibial artery were not palpable; an indolent ulcer was present on the dorsal surface of the second toe. Note the rarefaction of the bones. The roentgenographic appearance is suggestive of Sudeck's "acute atrophy." Compare this roentgenogram with figure 1. The rarefaction shown in figure 1 was due to the resorption and erosion of necrotic bone.

diabetic patients with arteriosclerosis and gangrene are so predisposed to extensive infection that if amputation is delayed for a considerable time, the badly devitalized bone, because of infection, is a potential infected sequestrum and therefore is not regenerated. In arteriosclerotic

patients, therefore, some degree of chronic atrophy is likely to be encountered roentgenographically in the absence of frank clinical gangrene and infection, which complicate the picture.

No cases of thrombo-angiitis obliterans are included in this histologic study, as none were available for examination. This further attests to the value of the conservative medical treatment that has been given these patients within the last few years. We have, however, seen roentgenograms of the feet of many such patients with impending gangrene or with marked circulatory disturbance without gangrene; these bones are prone to show the spotted, punctate appearance (fig. 10). Since we have not had bones of this sort under histologic observation, we cannot say with certainty what conditions such roentgenographic manifestations; it seems fair, however, to infer that the spotted appearance is the result of substitution of new bone for devitalized bone by the process of creeping replacement, and that the shadows which are due to increased permeability are the result of cortical erosion and enlargement of spaces in the vessel canal.

#### BONES OF EXTREMITIES AFFECTED BY ACUTE VASCULAR OCCLUSION

It is well known that obstruction of an otherwise normal artery supplying an extremity need not lead to necrosis and gangrene of the part. If circulatory interference has been severe, the histopathologic changes in the bones will depend on the completeness of the circulatory interruption, the length of time that elapsed between the onset of the gangrene and the amputation and the degree of circulatory restoration that had been spontaneously inaugurated. Thus, when there is prompt amputation, the histopathologic examinations may in certain instances disclose extensive or little necrosis of the bone, but in any event the roentgenographic studies will demonstrate that such bone casts rather normal shadows. On the other hand, if injury to the tissue has been severe but considerable circulatory restoration has delayed the amputation for a long time, both roentgenographic and histopathologic changes are observed.

The approach by experimental study to more definitive information as to the effects of acute vascular occlusion on the soft tissues and bones of the extremities has not been productive of much enlightenment. It has proved extremely difficult to produce gangrene in an extremity of an experimental animal through vascular occlusion; to do so, one must eliminate the possibility of the development of a sustaining collateral circulation; in normal animals, the absence of serious functional impairment at the time of ligating the vessels makes the prognosis good as regards viability of the part. The following experimental examples attest to the great difficulty of producing changes in the bone in the

adult animal or of influencing the growth of the bones of a younger animal. Latarjet<sup>3</sup> ligated the femoral artery in young rabbits, while in still younger rabbits he ligated the femoral artery and destroyed the nutrient vessel of the tibia; in spite of these procedures, he observed no disturbances in the growth of the bones in any of his animals; the obturator arteries became the main source of arterial supply to the extremities on which operation had been performed. Grey and Carr,<sup>4</sup> working with dogs and rabbits (of no stated age), concluded that venous congestion through occlusion of a large vein led to no recognizable changes in the bone structure of the parts on which operation had been performed; while local anemia due to arterial ligation likewise occasioned no atrophies of the bone as long as the part remained functionally active; these conclusions were based solely on roentgenographic studies. In ligating in rabbits the external iliac artery or vein or both simultaneously, Benassi<sup>5</sup> found no changes in the growth or in the histologic and roentgenographic appearances of the bones; some of the animals were adults and others about 1 month of age at the time of operation.

However, Brooks and Martin<sup>6</sup> induced gangrene in the lower extremities of about 72 per cent of their rabbits when the common iliac and external iliac arteries were ligated proximal and distal to the origin of the hypogastric artery. In a second series in which there was added to this procedure ligation of the common iliac vein, the incidence of gangrene was only about 33 per cent. Holman and Edwards<sup>7</sup> also observed that when the common iliac artery and inferior vena cava were simultaneously ligated in eighteen rabbits, gangrene developed twice, while in ten rabbits in which the common iliac and external iliac arteries and the inferior vena cava were simultaneously obstructed gangrene did not occur.

Only when an experimental vascular obstruction is severe enough to produce gangrene of the soft parts are changes in the bone also clearly manifest; at such times, necrosis of the bone results. With frank, irreparable gangrene of a part, all of the tissues die and consequently nothing special can be said concerning the distinctive behavior of such bones under experimental conditions. Burckhardt's<sup>8</sup> experiments shed little additional light on this subject; he wound an elastic band as tightly

3. Latarjet, A.: *Compt. rend. d. l'Assoc. d. anat., supp.*, 1912, p. 72.

4. Grey, E. G., and Carr, G. L.: *Bull. Johns Hopkins Hosp.* 26:381, 1915.

5. Benassi, E.: *Arch. ital. di chir.* 28:49, 1931.

6. Brooks, B., and Martin, K. A.: *Simultaneous Ligation of Vein and Artery*, J. A. M. A. 80:1678 (June 9) 1923.

7. Holman, E., and Edwards, M. E.: *New Principle in Surgery of Large Vessels; Ligation of Vein Proximal to Site of Ligation of Artery; Experimental Study*, J. A. M. A. 88:909 (March 19) 1927.

8. Burckhardt, H.: *Beitr. z. klin. Chir.* 138:625, 1926-1927.

as possible around the forelegs above the wrists of rabbits from 3 to 4 months old, the elastic being permitted to remain for various lengths of time up to more than twelve hours; after twelve hours, complete necrosis of the part occurred; many of the animals bandaged for less than twelve hours showed paralysis, ulceration and complete loss of hair in the affected part; the damage to the part was on the whole proportional to the length of time the elastic was applied. On the basis of histologic examinations, Burckhardt believed that he could demonstrate by these experiments a greater sensitiveness of the bone to vascular injury, as the necrosis of the bone was observed long after all traces of the injury to the soft parts had disappeared. In the regeneration of bone, the necrotic portions underwent creeping replacement (it is interesting that Burckhardt made no particular mention of lacunar resorption); most of the regeneration was from the marrow side, with formation of endosteal bone. It is worthy of comment, in connection with the theme of this paper, that Burckhardt found roentgenologic study of the extremities of no value in drawing conclusions concerning conditions of the bone during regeneration. Therefore, all that can be gleaned from these experiments is that when bone and marrow are seriously but not irreparably injured by circulatory obstruction, regeneration of bone proceeds surely but more slowly (as is natural) than regeneration of the soft parts.

The bones of the right lower extremity of a colored man, aged 45, demonstrated the extent to which changes of the bone may proceed after acute vascular occlusion.

CASE 6.—While walking the patient suddenly experienced pain in the right lower extremity, which began on the inner aspect of the sole and radiated as high as the middle of the thigh. The sudden attack of pain was immediately followed by a feeling of numbness from the knee down. As the patient expressed it, the extremity "felt dead," and it was unable to bear weight. Five months later he was admitted to the hospital, when the right lower extremity was atrophic; femoral arterial pulsation was not palpable; the blood pressure in the involved extremity was 0 systolic and 0 diastolic, while in the left lower extremity it was 180 systolic and 96 diastolic; there were paresthesia and coldness of the diseased limb but no gangrene; the Wassermann test of the blood was negative. All of the indications (including a roentgenogram of the pelvis which showed a shadow in the region of the right common iliac artery) pointed to the existence of a thrombus in the common iliac region, possibly at the bifurcation of the aorta, the clot straddling this region. Collateral circulation was adequate to prevent gangrene, though not sufficient for normal nutrition, for pain in the extremity was becoming progressively worse.

Roentgenograms of the bones of the extremity revealed extensive changes; disseminated throughout were areas of rarefaction involving both cortical and spongy bone; these presented themselves as round or somewhat elongated shadows, the result of increased permeability to radiation. In addition, the bones everywhere cast a less dense shadow than normal. The anterior portion of the femoral cortex was particularly rarefied (figs. 1 and 9).

The existence of a generalized lymphadenopathy prompted the removal of a gland from the right inguinal region; the day following, a burning sensation developed in the right foot; four days later, trophic disturbances over the foot were more marked; within ten days, ulceration of the skin at the base of the great toe appeared; within three weeks definite dry gangrene of the large toe and of the third and fourth toes with superficial ulceration was manifest; five weeks after this, biopsy and an amputation at the midhigh were performed.

Dissection of the specimen, which consisted of the right foot and leg and the lower 8 inches (20.32 cm.) of the femur, disclosed an extremely marked atrophy of the soft tissues. The large toe was gangrenous to the metatarsal phalangeal joint, and this was the condition in regard to the other toes. Dissection of the anterior and posterior tibial arteries showed that neither they nor the branches were occluded; the lumen of the popliteal artery was patent; this was likewise the case in regard to the portion of the femoral artery that came with the specimen. On histologic study, the vessels were found to have thickened walls, while some of them, particularly the popliteal artery, showed considerable medial sclerosis and intimal thickening, but none of the vessels in the regions examined showed evidences of thrombosis or recanalization. The muscles of the calf were extremely atrophic, while the muscles of the foot were somewhat infected.

When the muscles and periosteum were stripped from the amputated portion of the femur, enlargement of the longitudinally directed vascular canals was apparent, and thinning of the anterior portion of the cortex was obvious. When this bone was opened longitudinally, it was seen that the marrow cavity was enlarged from the endosteal side; the spongy trabeculae were definitely thin, and the marrow was fatty. Longitudinal sectioning of the tibia revealed atrophy in its upper third; the spongified diaphyseal cortex measured as much as from 10 to 12 mm. in thickness. The astragalus and calcaneus on section were atrophic and fatty. The toes showed gangrene and infection of the soft tissues and osteomyelitis and necrosis of the phalanges and possibly of the heads of the metatarsal bones.

Histologic examination of the femoral cross-sections demonstrated widespread aseptic necrosis; the original compacta (from periosteal to endosteal surfaces) was almost entirely dead. Some revascularization of the dead bone was in evidence, and as a result numbers of haversian canals were much enlarged; through fusion, some of the enlarged ones had produced wide haversian spaces; the widened, revascularized canals and spaces were lined by newly deposited bone and were filled with a loosely cellular connective tissue containing numerous blood channels (fig. 11 *A* and *B*). Extensive necrosis of the compacta was likewise apparent in tibial cross-sections, the innermost portions staining most poorly; resorption and revascularization were occurring from the periosteal side. The fatty marrow was edematous.

On histologic section the calcaneus evidenced extensive necrosis of the trabeculae and degeneration of the associated fatty marrow; however, evidences of revascularization of the marrow were to be found. The revascularized marrow contained deposits of new bone on the walls of some of the trabeculae; other trabeculae seemed to have undergone revivescence as a result of the revascularization. Here and there, the fragmentary formation of connective tissue bone in the marrow was noticeable. To a great degree, the astragalus illustrated similar microscopic pictures. While its articular cartilage still showed nuclear staining, the thick subchondral trabeculae were for the most part completely necrotic. Revascularization of the astragalus was in progress; some of the original trabeculae were in the process of resorption, and some of the necrotic marrow was being invaded by considerable granulation tissue.

The metatarsal bones were virtually completely necrotic, but regeneration was in progress, particularly from the periosteal side; new blood vessels and connective tissue had led to enlargement of existing vessel canals and erosion of the subperiosteal bone. Likewise, slight revascularization of the necrotic marrow had occurred, with the appearance of numerous new vessels in certain portions. The

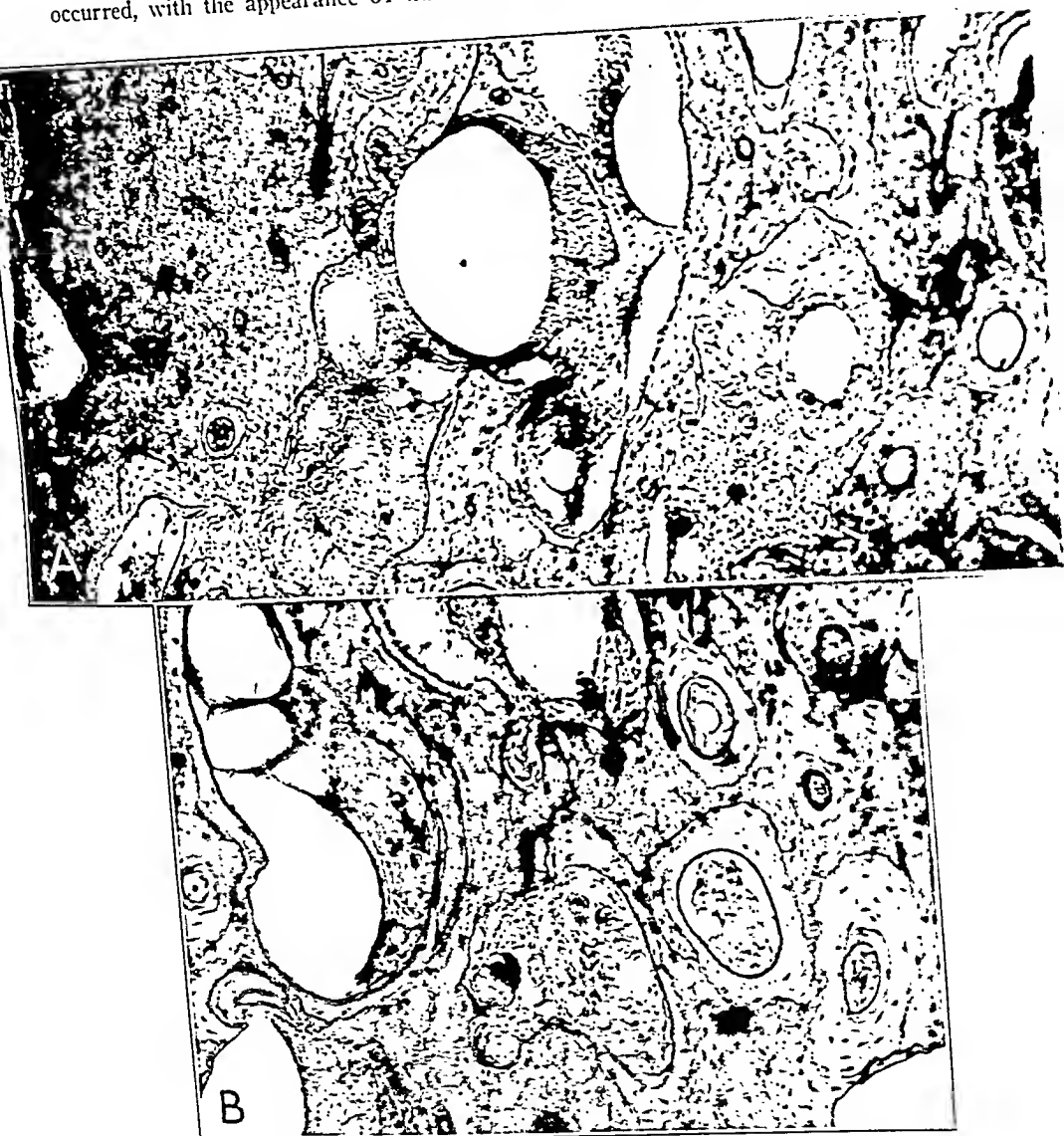


Fig. 11.—*A*, the femoral cortex in cross-section, demonstrating revascularization of dead bone; the haversian canals are enlarged; through fusion, wide haversian spaces have appeared. Much of the bone between these spaces was dead. It is plainly evident why the roentgenogram of the femur shows marked rarefaction (fig. 9);  $\times 30$ . *B*, a higher magnification of an area represented in figure 11 *A*. The enlarged spaces are lined by newly deposited bone and are filled by loosely cellular connective tissue containing numerous newly formed blood channels;  $\times 150$ .



articular cartilages of these bones were, on the whole, well retained (fig. 12). The phalanges demonstrated similarly that the original bone had undergone extensive or complete necrosis and that revascularization was actively in progress. The microscopic changes in the bones of the feet made explicable the roentgenographic appearances; the linear and oval shadows of increased permeability to light were the result of the resorption of the originally necrotic bone.

However, when revascularization, resorption and osseous transformation are slow in appearing or do not proceed to a considerable degree before amputation is performed, the roentgenogram of a gangrenous extremity may show essentially negative results, although bone necrosis may be widespread. This is confirmed by the examination of the right foot and leg in the following case:

CASE 7.—A man, aged 26, was apparently entirely well until five weeks before admission to the hospital; at that time, cough and fever appeared. Two weeks before admission, he suddenly felt that his right foot was numb, cold and heavy,

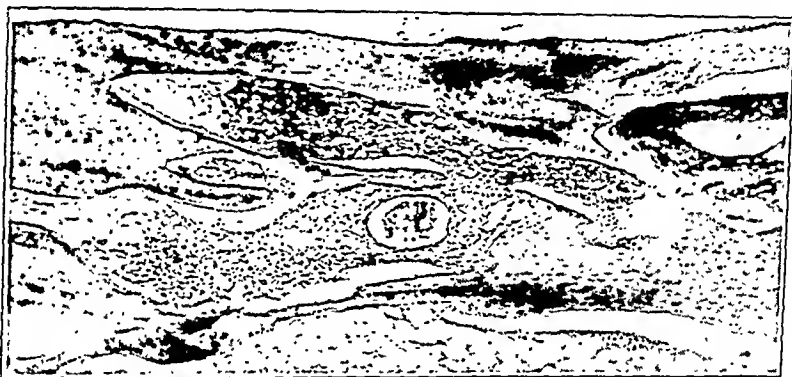


Fig. 12.—The necrotic and rarefied cortex of the fifth metatarsal bone is shown. The cortex is thin, and the enlarged spaces are filled with inflammatory exudate (compare with figure 1);  $\times 30$ .

without attendant pain; the toes also blanched. At admission, the toes of the right foot were black, and there were two red-black areas on the leg with lymphangitis; a blood culture was sterile; the blood sugar was normal. Amputation was performed two weeks after admission, or one month following the onset of the symptoms in the extremity.

The specimen consisted of the lower 6 inches (15 cm.) of the femur and the leg, and foot; a dry gangrene involving all of the toes and extending ventrally to the heel and dorsally over half of the surface of the foot was revealed. On the dorsum of the foot there was a line of demarcation above which the tissues were not black but discolored red; at the line the skin was interrupted. Posteriorly, the gangrene extended up from the heel to about the middle of the leg, where there was a sharp dividing line; at this line the skin was again interrupted. The demarcating line observed exteriorly was likewise seen in the muscles of the leg; the muscle in the gangrenous area was grossly degenerated and disorganized; in certain zones it was greenish and in others hemorrhagic, while that above the gangrenous level retained the pink color. Some of the popliteal vessels were occluded by relatively fresh thrombi, which extended into the posterior tibial vessels; the anterior tibial

vessels, wherever traced, were found to be free from thrombi; no pockets of pus were found between any of the muscle bundles, although the tissues of the leg and foot had a foul odor.

Histologic study of the vessels demonstrated that the oldest process was in the posterior tibial artery; in this vessel there was evidence of complete recanalization of an organized thrombus. The sections further disclosed that the popliteal artery was more recently plugged; there were only slight organization and evidence of recanalization. Furthermore, the popliteal and posterior tibial veins were also thrombosed, and organization of the thrombi with recanalization was advanced in the posterior tibial tributaries. The histologic examination materially aided in interpreting the clinical phenomena that had occurred: First, there was closure of the posterior tibial artery by a thrombus; by then an adjustment period of about two weeks elapsed, and a phlebitis appeared. The phlebitis was migratory, and there was further extension of the arterial occlusion, resulting in the gangrene of the toes evident on admission of the subject. Finally, a spreading infection with lymphangitis necessitated amputation before the appearance of frank pus.

The soft tissues were dissected from the bones, and these were examined by roentgen rays. It was surprising to find that in spite of the extensive changes in



Fig. 13.—Roentgenogram of a sagittal section of the foot of a young man, aged 26, who suffered from acute arterial occlusion. The soft tissues of the foot showed extensive gangrene. None of the bones demonstrated are roentgenographically abnormal.

the soft tissues of the foot, the bones appeared roentgenographically normal; they also cut with normal resistance (fig. 13). The roentgenogram of the tibia disclosed a cortex of normal thickness, but there was slight rarefaction in portions of it, which was definitely the result of enlargement of vessel canals; the upper and lower ends of this bone showed no roentgenographic abnormalities. The fibula was likewise roentgenographically normal.

Further gross examination of the bones revealed no striking abnormalities, except that the marrow of the navicular bone was greenish yellow; the marrow of the cuboid was partly hemorrhagic; the marrow of the phalanges of the large toe was much discolored by blood; the same discoloration, to a lesser degree, was to be observed in the marrow of the first metatarsal bone; the condition in the other toes was comparable to that in the large toe. The other bones presented nothing abnormal in the gross, except that the marrow of the lower ends of the tibia and fibula was somewhat injected.

The histologic examination of the terminal phalanx of the large toe disclosed that its basal half was completely necrotic; this necrosis involved the articular

cartilage, medullary fat and surrounding soft tissues. However, the most distal half of the bone showed retention of the bone cell nuclei in most of the cortical area and in the spongy trabeculae, although the bone cell nuclei were pyknotic. This was entirely in keeping with the conditions in the surrounding soft tissue, which demonstrated a considerable number of staining nuclei and numerous dilated and engorged vascular channels—apparently of some nutritional potency. The proximal phalanx was virtually entirely necrotic, this being so with regard to the articular cartilages, the marrow and the spongy and cortical bone. In neither the distal nor the proximal phalanx was there evidence of revascularization of the bone or marrow; the necrotic bone represented the original bone without structural modification; the nuclei retaining stainability were those situated fortunately so as to receive nourishment. With regard to the first metatarsal bone, the conditions were practically identical: The marrow, cortex and spongy bone throughout were dead, and there was no revascularization. The histologic study of these bones clarifies the significance of the apparently normal roentgenographic appearance; the bones had died without any modification of their density, thereby casting the same shadow that they would have cast during life.

Roentgen examination of the other bones of the foot also for the most part gave negative results, but histologic study disclosed necrosis of the osseous and marrow tissue of these tarsal bones or of their parts that were surrounded by necrotic soft tissue. Wherever infection was superimposed, the necrosis was more pronounced. As observed in the large toe, there was no significant evidence of revascularization, resorption or osseous transformation in the necrotic zones. The tibia and femur, on histologic examination, reflected the same general observations.

#### SUMMARY AND CONCLUSIONS

The object of this work was to inquire into the nature of the microscopic changes occurring in the bones of gangrenous extremities resultant from vascular occlusion; particular attention was paid to the state of the bones at some distance above the level of gangrene and infection. Another phase of the investigation had special emphasis—the correlation of the gross and microscopic changes with any changes revealed on roentgenographic study of these bones. Apparently, Mueller alone had made somewhat similar histologic studies, in which he stressed extensive necrosis of the cells of the cortical interstitial lamellae as the only direct effects of circulatory disturbance due to arteriosclerosis. Undoubtedly the cells of the cortical interstitial lamellae have a marked tendency to die. Even in the absence of gangrene, this predisposition was evidenced in femoral cross-sections of our control specimens. These controls were taken from patients ranging from 8 to 62 years of age, who died from various causes. Thus, this tendency toward degeneration and death of the cells of deeply situated lamellae of compact bone is to be considered a normal characteristic, progressively increasing with age; in arterio-

sclerosis with gangrene it is more marked in the bone high above the gangrenous level; roentgenographically, this feature alone does not result in the appearance of abnormal shadows of bone.

When chronic vascular disease has persisted for any length of time before gangrene evolves, the marked and native disposition toward the development of collateral circulation frequently reduces to secondary importance the vascular obstruction factor per se as regards the production of changes in the bone. Although therapy may have for months staved off the necessity for amputation, the long interval of time has permitted such factors as infection, inactivity and so-called trophomenotic influences to exert themselves on the bones. Thus, dependent on whether or not and to what extent these influences are brought into play, roentgenographic changes are present or absent in the bones, although they may show definite microscopic changes (particularly, extensive death of the interstitially placed bone). Six specimens of chronic vascular disease with gangrene illustrated the absence of specific and characteristic roentgenographic changes as a result of chronic vascular obstruction. This study marked more clearly the need for understanding the microscopic changes in order to interpret properly any roentgenographic evidence of changes in the bone. It was pointed out that the bones of a gangrenous toe, although appearing roentgenographically normal, may on histologic examination evidence osteomyelitis; the absence of periostitis in the roentgenogram is explicable by the devitalization of the soft tissues about the bones. Furthermore, if a devitalized bone is revascularized through circulatory readjustments, the resorption and reconstruction will be demonstrated roentgenographically by punctate shadows of increased permeability; they are the result of enlargement of earlier vascular canals and cortical erosion (particularly from the periosteal side). Diabetic patients with arteriosclerosis and gangrene are so predisposed to extensive infection that their necrotic bones, becoming potentially infected sequestrums, show less tendency toward revascularization.

One case is reported of high, acute, vascular occlusion with a long delay in the appearance of gangrene. Collateral circulation was adequate to prevent gangrene, though not sufficient for normal nutrition. Roentgenograms of the bones of the extremity five months after the onset of the vascular occlusion revealed extensive changes; there were areas of rarefaction disseminated throughout and exhibited in round or somewhat elongated shadows, everywhere less dense than normal. Histologic examinations of the bone high above the gangrenous level disclosed the

existence of widespread, aseptic necrosis, the original compacta of the femur being almost entirely dead. Revascularization of the dead bone was in evidence and therefore numbers of haversian canals were greatly widened, still more so through the fusion of some of them; the new spaces were lined by newly deposited bone and contained loosely cellular connective tissue with numerous blood vessels. Extensive necrosis of the compacta of the other bones was likewise in evidence. The roentographic appearance here was essentially due to the revascularization of dead bone.

# SEQUENCES OF EXPERIMENTAL INFARCTION OF THE FEMUR IN RABBITS

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A number of lesions, etiologically obscure but with certain characteristics in common, have been described in various bones. The onset and clinical progress are insidious and may or may not be associated with trauma. In these lesions there is a gradual and progressive destruction of the tissues of the bone, as demonstrated in roentgen films and by examination of tissue. The parts involved are almost always in an epiphysis or in epiphyseal cartilage, and ultimately a deformity of the bone results. These various lesions have been designated osteochondritis, anemic infarction, epiphysitis or aseptic necrosis of bone, terms which imply some vascular or nonspecific disorder not clearly understood. Among the more important specifically named disturbances of this group are: aseptic or anemic necrosis of the head of the femur, radius or humerus or distal epiphysis of the femur; König's osteochondritis dissecans of the medial condyle of the femur; osteochondritis deformans juvenilis of Perthes, Legg and Calvé; Osgood-Schlatter's disease of the tibial tubercle; Sudeck's acute atrophy of bone; necrosis of the tarsal navicular bone (Köhler's disease), of the bodies of the vertebrae (Kümmell's disease), of the head of the metatarsal bones (Freiberg's disease, also described by Köhler) and of the carpal semilunar bone (Kienböck's disease), and occasional foci in many other bones, particularly of the lower extremity.

The cause of these necroses is not understood, and the etiologic factors concerned have been hypothecated rather than actually demonstrated in the diseased tissues. In view of the occasional bilateral occurrence and the incidence of these lesions of bone in several members of a family, a hereditary tendency is assumed by some to be a factor (Bernstein).<sup>1</sup> Since these lesions are frequently present in a bone near a joint, the trauma of weight bearing and muscle tension have been

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1. Bernstein, M. A.: Osteochondritis Dissecans, *J. Bone & Joint Surg.* 7:319, 1925.

considered important (Geyman,<sup>2</sup> Kappis<sup>3</sup> and Dürig<sup>4</sup>), and many consider that external trauma, probably associated with a local vascular disturbance, is the chief factor. The most plausible explanation yet offered seems to be a primary alteration of the normal nutrition in a region of bone followed by or associated with trauma or a mild infectious agent.

Following an exhaustive study of the various forms of necrosis of bone, all of which he considered to be fundamentally alike, Axhausen<sup>5</sup> stated that these are bland anemic infarcts of bone produced by mycotic emboli. This opinion is hypothecated, because Axhausen assumed that attenuated organisms are present. The possibility of a vascular nutritional disturbance being an important primary etiologic factor has gained considerable credence and has been emphasized in the more recent clinical and experimental studies. Phemister<sup>6</sup> supported the theory of infarction, but considered this alone insufficient to produce the marked changes usually present. Phemister, Brunnschwig and Day<sup>7</sup> cultivated successfully a streptococcus from the necrotic marrow tissues of two bones with Kienböck's disease, one with Perthes' disease and one with Köhler's disease. Attempts to reproduce such lesions by the intravenous injection of pyogenic organisms were unsuccessful. In his original report on osteochondritis dissecans, König<sup>8</sup> considered trauma alone insufficient to produce the changes and believed that the loose bodies in the knee joint were probably sequestered infarcted bone. In a symposium of twelve articles<sup>9</sup> by Legg, Calvé, Moreau and others, the general opinion was expressed that the principal site of osteochondritis juvenilis is the epiphyseal line and that the etiology is unknown, but is probably associated with a mild infection or a disturbance of circulation. In a more recent survey of opinions, Perthes<sup>10</sup> concluded that internal

2. Geyman, M. J.: Osteochondritis Dissecans, *Radiology* **11**:315, 1928.

3. Kappis, M.: Osteochondritic Dissecans, *Deutsche Ztschr. f. Chir.* **171**:13, 1922.

4. Dürig, A.: Beitrag zur Aetiologie der Köhlerschen Krankheit, München. med. Wchnschr. **70**:362, 1923.

5. Axhausen, G.: Ueber anämische Infarkte am Knochensystem und ihre Bedeutung für die Lehre von den primären Epiphyseonekrosen, *Arch. f. klin. Chir.* **151**:72, 1928.

6. Phemister, D. B.: Newer Knowledge of Pyogenic Infection of Bone, *Proc. Inst. Med. Chicago* **7**:169, 1929.

7. Phemister, D. B.; Brunnschwig, A., and Day, L.: Streptococcal Infections of the Epiphyses and Short Bones, *J. A. M. A.* **95**:995 (Oct. 4) 1930.

8. König, F.: Ueber freie Körper in den Gelenken, *Deutsche Ztschr. f. Chir.* **27**:90, 1887.

9. Symposium: Legg, A.: *Arch. franco-belges de chir.* **25**:585 (April) 1922. Calvé, J.: *Arch. franco-belges de chir.* **25**:592 (April) 1922. Moreau, J.: *Arch. franco-belges de chir.* **25**:652 (April) 1922.

10. Perthes, G.: Ueber Osteochondritis deformans coxae, *Klin. Wchnschr.* **3**: 513, 1924.

factors cause a change in the epiphyseal cartilage of the head of the femur, and the accidental lesion of a blood vessel leads to necrosis. Hirsch and Ryerson,<sup>11</sup> in a report on marked necrosis of the distal epiphysis of the femur, emphasized the long duration and progressive destruction of the bone without attempt at repair in these lesions. They believed the primary cause to be one of vascular occlusion. The anatomic position of metastatic subchondral and metaphyseal foci of osteomyelitis is often attributed to occlusion of end-arteries by infected emboli. According to Nussbaum,<sup>12</sup> the diaphysis of long bones can resist such foci of infection because of an abundant collateral blood supply.

There are many reports and discussions on so-called aseptic necrosis of the head of the femur associated with or following dislocation of the head or intracapsular fracture of the neck of the femur. Some necroses are also associated with so-called slipping of the upper epiphysis of the femur. The consensus is that such necrosis is the result of a nutritional disturbance, usually from injury to the blood supply carried in the ligamentum teres femoris.

Many physiologic and anatomic factors must be considered in order to appreciate the full significance of necrosis in bone and the great difficulty attending its study. Important among these are: (1) the general circulatory pattern, (2) the relative importance for normal nutrition of the various sources of blood and (3) the presence or absence of end-arteries and anastomoses. Because of the great vascularity of bone, experimental division of a vessel does not, except in isolated instances, simulate occlusion of the endings of that vessel by emboli.

The evidence at present favors the opinion that the bone marrow tissues in mammals have a closed vascular system, that is, arterial and venous blood flow in defined channels with distinct endothelial linings (Sabin<sup>13</sup>), and that some regions are different from the general pattern because they are nourished by a certain vessel or group of vessels of common origin. There are four chief sources of arterial blood in long bones: (1) the principal and occasional accessory nutrient arteries to the shaft; (2) small vessels that pierce the cortex to enter the metaphyseal ends of the shaft; (3) periosteal twigs that enter the cortical bone, and (4) small but distinct epiphyseal vessels, including those of the femur that are carried by the ligamentum teres and those that enter at the attachment of a joint capsule. The ramification and anastomosis of these vessels in growing bones probably is altered by the presence

11. Hirsch, E. F., and Ryerson, E. W.: Necrosis of the Distal Epiphysis of the Right Femur, *J. A. M. A.* **93**:679 (Aug. 31) 1929.

12. Nussbaum, A.: Beziehungen der Knochengefäße zur akuten Osteomyelitis, *Zentralbl. f. Chir.* **49**:700, 1922.

13. Sabin, F. R.: Bone Marrow, *Physiol. Rev.* **8**:191, 1928.



of epiphyseal cartilage plates. Johnson<sup>14</sup> studied the relative importance of these systems to the normal nutrition of the shaft of the tibia in dogs by determining the rate of osseous repair in drill holes and the distribution of india ink in the medullary tissues after interruption of one or two sources by division of the vessels. He concluded that the nutrient artery supplied the medulla and the inner portion of the cortex and was sufficient alone to maintain normal viability of the tissues of the shaft; that the metaphyseal vessels would supply enough blood to the shaft to prevent necrosis but not to promote repair, and that the periosteal twigs supplied only the outer two thirds or one half of the cortex and formed very few anastomoses with the medullary channels. He did not consider the age of the animals and the possibility of epiphyseal collateral circulation to the shaft. Using the experimentally fractured fibulas of dogs, Pearse and Morton<sup>15</sup> observed no impairment in healing after division of the nutrient vessel, owing to rapidly developed collateral circulation. Moore and Corbett,<sup>16</sup> however, could not obtain healing in experimental fractures after the nutrient artery was ligated. On the other hand, according to McWilliams,<sup>17</sup> Kolodny,<sup>18</sup> Haldeman<sup>19</sup> and Gallie and Robertson,<sup>20</sup> the periosteal blood supply to the shaft is most important. These divergent views indicate that more attention should be given to the collateral circulation and that experimental procedures more than interruption of the arteries must be used. Brunschwig<sup>21</sup> produced infarction of the tibia of young dogs by stripping the entire shaft of its periosteum and presumably tearing the nutrient artery. This did not occur in adult animals, which demonstrates the important collateral circulation to the shaft that develops from the epiphyses after the cartilage lines close. Continuity of epiphysis and diaphysis, established by obliteration of the epiphyseal lines, may account for the infrequency of foci in adult bones comparable to metaphyseal foci of infection and necrosis in growing bones.

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14. Johnson, R. W., Jr.: A Physiological Study of the Blood Supply of the Diaphysis, *J. Bone & Joint Surg.* **9**:153, 1927.

15. Pearse, H. E., Jr., and Morton, J. J.: The Influence of Alterations in the Circulation on the Repair of Bone, *J. Bone & Joint Surg.* **13**:68, 1931.

16. Moore, J. E., and Corbett, J. F.: Studies on the Function of the Periosteum, *Surg., Gynec. & Obst.* **19**:5, 1914.

17. McWilliams, C. A.: The Periosteum in Bone Transplantations, *J. A. M. A.* **62**:346 (Jan. 21) 1914.

18. Kolodny, A.: The Periosteal Blood Supply and Healing of Fractures, *J. Bone & Joint Surg.* **5**:698, 1923.

19. Haldeman, K. O.: The Role of the Periosteum in Healing of Fractures: Experimental Study, *Arch. Surg.* **24**:440 (March) 1932.

20. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, *Brit. J. Surg.* **7**:211, 1919.

21. Brunschwig, A.: Experimental Infarction of Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* **27**:1049, 1930.

The importance of the ligamentum teres to a normal blood supply in the head of a femur depends on the ability of that bony epiphysis to develop collateral circulation. Müller,<sup>22</sup> Freund,<sup>23</sup> Speed,<sup>24</sup> Wolcott,<sup>25</sup> Santos,<sup>26</sup> Chandler and Kreuscher<sup>27</sup> and many others, after clinical studies and gross and microscopic examination of the ligamentum teres in cadavers and in tissues removed at operation, stress its need for the prevention of necrosis of the head of the femur such as may follow dislocation or fracture. Kolodny<sup>28</sup> took another view, since he demonstrated the intracapsular periosteum and periosteal blood supply of the neck of the femur to be the same as elsewhere. If the proximal epiphyseal line is closed so that there is medullary continuity between the head of the epiphysis and the shaft, destruction of the ligament should do no harm. If, however, this continuity is interrupted above the brim of the articular cartilage, whether the line is open or closed, and the ligamentum teres is ruptured, the proximal fragment will be severed completely from its blood supply. Thus, necrosis of the head of the femur may occur at any age and should not be confused with osteochondritis juvenilis, which is primarily a disturbance in the open proximal epiphyseal line of growing bones.

Without good experimental evidence, end-arteries are assumed to be present beneath open epiphyseal plates, and articular cartilages and medullary tissues otherwise are considered to have a dense meshwork of active and potential arterioles and capillaries. This is probably the basis for the frequent occurrence of metaphyseal and subchondral metastatic infections and necroses. According to Johnson and Kolodny, Lexer and Kuliga<sup>29</sup> thought that the branches of the nutrient artery

22. Müller, W.: Experimentelle Untersuchungen über Nekrosen und Umbauprozesse am Schenkelkopf nach traumatischen Epiphysealungen und Luxationen und ihre klinische Bedeutung, Beitr. z. klin. Chir. **132**:490, 1924.

23. Freund, E.: Zur Frage der aseptischen Knochennekrose, Virchows Arch. f. path. Anat. **261**:287, 1926.

24. Speed, K.: Fracture of the Neck of the Femur, Ann. Surg. **96**:951, 1932.

25. Wolcott, W. E.: Circulation of the Head and Neck of the Femur: Relation to Nonunion in Fractures of the Femoral Neck, J. A. M. A. **100**:27 (Jan. 7) 1933.

26. Santos, J. V.: Changes in the Head of the Femur After Complete Intracapsular Fracture of the Neck: Their Bearing on Nonunion and Treatment, Arch. Surg. **21**:470 (Sept.) 1930.

27. Chandler, S. B., and Kreuscher, P. H.: A Study of the Blood Supply of the Ligamentum Teres and Its Relation to the Circulation of the Head of the Femur, J. Bone & Joint Surg. **14**:834, 1932.

28. Kolodny, A.: The Architecture and the Blood Supply of the Head and Neck of the Femur and Their Importance in the Pathology of Fractures of the Neck, J. Bone & Joint Surg. **7**:575, 1925.

29. Lexer, E., and Kuliga, P.: Untersuchungen ueber Knochenarterien mittelst Roentgenaufnahmen injizierter Knochen und ihre Bedeutung fuer einzelne pathologische Vorgaenge am Knochensysteme, Berlin, A. Hirschwald, 1904.

extend to but do not pierce the open epiphyseal lines or anastomose with the vessels of that region entering through the cortex until after growth has ceased. It seems logical to consider that such a region depending on one source of blood is, in reality, a region with so-called end-arteries. Kolodny, however, stated that some of these metaphyseal branches of the nutrient artery pierce the epiphyseal line and enter the bony epiphysis (described for the head of the femur), and thus the metaphysis may draw blood from the epiphysis. Freiberg<sup>30</sup> called attention to the *arteria genu media* which arches over the posterior central ligament and the internal condyle of the femur. He stated that it is frequently terminal and if blocked will produce osteochondritis dissecans, as described by König.

Attempts to produce infarcts of bones experimentally in animals have aided little in understanding the clinical disorders mentioned. These attempts, however, have emphasized the necessity of adequate nutrition for normal vitality. Axhausen<sup>31</sup> produced necrosis of bone by the use of heat, cold and tincture of iodine, and Phemister<sup>32</sup> obtained similar death of tissues and reactive changes with radium. Bancroft<sup>33</sup> studied necrosis, sequestration and involucrum formation in the humerus of dogs following intramedullary injections of croton oil. He emphasized the importance of the blood supply to the regeneration of bone. Using the head of metatarsals of growing dogs, Sacerdote<sup>34</sup> produced marked necrosis and deformity by removing the periosteum from a fractured segment. With removal of the periosteum or by fracture alone, the vascular changes and the resulting necroses were much less. Nussbaum<sup>35</sup> demonstrated necrosis and almost complete restoration of epiphyseal ossifying centers after destruction of the blood supply to the epiphyses. Partial necrosis and slight flattening of the head of the femur near the fovea were produced in young goats by Graham,<sup>36</sup> who attempted to reproduce osteochondritis juvenilis by destruction of the

30. Freiberg, A. H.: Osteochondritis Dissecans, *J. Bone & Joint Surg.* **5**: 3, 1923.

31. Axhausen, G.: Knochennekrose und Sequesterbildung, *Deutsche med Wchnschr.* **40**:111, 1914.

32. Phemister, D. B.: Radium Necrosis of Bone, *Am. J. Roentgenol.* **16**: 340, 1926.

33. Bancroft, F. W.: Bone Repair Following Injury and Infection, *Arch. Surg.* **5**:646 (Nov.) 1922.

34. Sacerdote, G.: Sulle conseguenze di interruzioni circolatorie e di fratture nelle epifisi di animali in accrescimento, *Chir. d. org. di movimento* **16**:291, 1931.

35. Nussbaum, A.: Die Arteriellen Gefäße der Epiphysen des Oberschenkels und ihre Beziehungen zu normalen und pathologischen Vorgängen, *Beitr. z. klin. Chir.* **130**:495, 1924.

36. Graham, R. V.: Experimental Considerations in Perthes' Disease (Division of Ligamentum Teres), *M. J. Australia* **1**:207, 1930.

ligamentum teres. By a similar procedure, Zemansky and Lippmann<sup>37</sup> caused considerable necrosis of bone and medullary tissues, flattening of the weight-bearing portion of the head and coxa vara deformity of the neck of the femur in young rabbits. They considered these changes to be very similar to those in Perthes' disease. Such changes did not follow interference with the ligamentum teres in adult rabbits, and from this they concluded that the ligament was not important for the nutrition of the femoral head after the cessation of growth. Stewart<sup>38</sup> could demonstrate no consistent changes in rabbits after division of the ligamentum teres. During an attempt to produce experimental arthritis in rabbits by the intravenous injection of pyogenic organisms, Jackson<sup>39</sup> demonstrated wedge-shaped infarcts of bone that were situated in the metaphyses with their bases close under the epiphyseal cartilage. This indicates that there are probably end-artries in the metaphyses and that they may be occluded by emboli.

In view of the paucity of experimental studies concerned primarily with necrosis and repair of bone, it seemed profitable to accumulate further data on the circulatory pattern of bone and the nature of infarcts in this tissue. Since simple ligation of vessels alone is unsatisfactory, because of the rapid formation of collateral circulation within the medullary tissues and outside the cortex, bland emboli were used so that small vessels would be occluded. Such a method also might elucidate the relative importance of the various sources of blood supply to a given portion of bone by a study of the nature and extent of the necrosis produced. If infarcts result, then a more applicable approach to the study of clinical entities involving necrosis has been formulated.

#### BLOOD SUPPLY TO THE FEMUR IN THE RABBIT

The femur in the rabbit has the usual small epiphyseal arterial twigs and periosteal blood supply. In addition, and far more important for normal nutrition, there are three principal vessels, all indirectly branches of the femoral artery. Two of these are branches of the profunda femoris which, in the rabbit, leaves the femoral artery at about the inguinal ligament and courses medially and downward. The first nutrient vessel leaves the profunda about 1.3 cm. from its origin (adult animal) and courses backward, inward and slightly upward to enter a large acetabular foramen in the ischium and become continuous with

37. Zemansky, A. P. Jr., and Lippmann, R. K.: The Importance of the Vessels in the Round Ligament to the Head of the Femur During the Period of Growth and Their Possible Relationship to Perthes' Disease, *Arch. Path.* 7:187 (Jan.) 1929.

38. Stewart, W. J.: Aseptic Necrosis of the Head of the Femur Following Traumatic Dislocation of the Hip Joint, *J. Bone & Joint Surg.* 15:413, 1933.

39. Jackson, L.: Experimental Streptococcal Arthritis in Rabbits, *J. Infect. Dis.* 12:364, 1913.

the vessels of the ligamentum teres. The second nutrient division arises 1 mm. or so distal to the first. It passes posteriorly to the medial edge of the lesser trochanter and then laterally across the lesser trochanter and posterior surface of the proximal end of the femur to enter the inferior angle of the trochanteric fossa with the tendon insertions of the short rotator muscles. Another, less significant, branch of the profunda femoris extends upward and backward to wind about the joint in the capsule near its attachment to the femur. This vessel probably supplies numerous small twigs to the adjacent bone and the greater trochanter. The third important vessel to the femur is the nutrient artery of the shaft which arises from the lateral circumflex artery near its origin from the femoral artery. It courses downward and backward to enter the nutrient foramen of the shaft on its medial surface near the linea aspera. These vessels probably vary in their details and anastomose freely with other vessels. In the many histologic preparations of the femur examined, only one epiphyseal vessel was noted to pierce an epiphyseal cartilage plate and enter the metaphysis. This small vessel, occasionally present in the plane of the sections examined, entered the upper end of the shaft from the greater trochanter and was constant in its position. Small periosteal twigs were more numerous where muscles and tendons attached, particularly on the posterior surface of the distal end of the shaft, and where the capsule of the hip joint inserted about the head of the femur. According to Piney,<sup>40</sup> the entire bone marrow of rabbits is cellular and penetrated by small vascular channels which, in long bones, branch from a central artery in the axis of the tissues.

#### EXPERIMENTAL METHODS

Infarction by embolism was produced by injecting a 2 per cent suspension of charcoal in physiologic solution of sodium chloride containing 5 per cent acacia into the nutrient arteries of the femur.<sup>41</sup> These particles of carbon were of the size that would pass through a sieve of 200 but not of 300 mesh per inch. Through an incision on the medial aspect of the thigh the femoral artery was exposed and ligated about 1 cm. distal to the origin of the lateral circumflex artery. The femoral artery proximal to the lateral circumflex artery and the lateral circumflex artery distal to the origin of the nutrient artery to the shaft of the femur were temporarily occluded by lifting ligatures. Small subcutaneous and muscle branches were ligated and cut. From 0.8 to 2 cc. of the suspension of charcoal was then slowly injected retrogradely into the femoral artery above the distal permanent ligature with a small gage needle, and afterward a second ligature was placed above the opening made in the vessel. This pro-

40. Piney, A.: *The Anatomy of the Bone Marrow: With Special Reference to the Distribution of the Red Marrow*, Brit. M. J. 2:792, 1922.

41. This method was used by Miller and Apfelbach in the infarction of renal glomeruli (*Experimental Infarction of the Glomeruli in Dogs*, Arch. Path. 4: 193 [Aug.] 1927). Dr. Apfelbach loaned me some of his apparatus.

cedure directed the suspension into the nutrient artery of the shaft. Before the needle was removed, sufficient suspension was withdrawn into the syringe to prevent occlusion of the femoral artery by carbon. Similar injections were made also with the proximal temporary ligature of the femoral artery placed above the origin of the profunda femoris so that carbon was allowed to enter the proximal end of the femur and the innominate bone through the branches of the profunda. The femoral artery of several of the legs, used as controls, was ligated without the injection of charcoal, but no attempt was made to equalize weight bearing. It is difficult to evaluate the possibility of some periosteal infarction through small twigs of vessels receiving carbon. Benassi<sup>42</sup> ligated the femoral and iliac arteries and veins separately and together, in growing and adult rabbits, and Pearse<sup>43</sup> removed the entire femoral artery in dogs without producing any noteworthy nutritional disturbances or functional disability of the leg.

A second approach to the study of changes in the bone, resulting from interference with normal nutrition, was by interrupting, at the site of entrance to the bone, one or a combination of vessels known to be distributed to the marrow tissues of the femur. The nutrient artery to the shaft was ligated through a small incision on the medial aspect of the thigh. Access to the ligamentum teres and the small vessel that enters the proximal end of the femur through the trochanteric fossa was obtained through an incision placed posteriorly over the hip joint with the leg adducted and rotated inward. During manipulation of the ligamentum teres there was moderate trauma to the articular surfaces and capsule of the hip joint. In no instance was there intentional interference with the periosteal blood supply.

The studies reported were made on the femurs of forty-six rabbits from 3 weeks to 2 years of age maintained on stock ration of oats and hay. Operative manipulations were performed with aseptic precautions under local infiltration of procaine hydrochloride or general anesthesia induced by pentobarbital sodium. The femurs were removed for examination from twenty hours to one hundred and fifty days after operation, cut into three segments (proximal, middle and distal thirds) and fixed in a dilute solution of formaldehyde, U. S. P. (1:10). After decalcification by 4 per cent solution of nitric acid, the segments were split longitudinally in such a way that the surfaces made would be of maximum size. Longitudinal sections of these tissues for histologic examination were prepared by the pyroxylin (celloidin) method and stained with hematoxylin and eosin. As an added check on the source of arterial blood to different portions of the femur, lithium-carmin and india ink were injected intravenously into some of the animals before death. In addition to the usual examinations, such preparations were studied grossly according to color distribution and microscopically in unstained preparations.

## RESULTS

The changes produced in the femurs of rabbits during a given period varied according to the age of the animals and the technical difficulties of injecting corresponding amounts of carbon in the same manner and probably also according to individual differences. Infarcts were readily

42. Benassi, E.: Lo sviluppo e trofismo dello scheletro degli arti in rapporto alla allacciatura dei vasi principali, *Arch. ital. di chir.* 28:49, 1931.

43. Pearse, H. E., Jr.: An Experimental Study of Arterial Collateral Circulation, *Ann. Surg.* 88:227, 1928.

produced by the injection of carbon alone, or in combination with rupture of an important nutrient vessel, but the necrosis was usually less marked and more poorly circumscribed when the circulation from one or more sources was interrupted external to the cortex without injection. The inability to control exactly the distribution of the carbon, owing to anastomoses of the nutrient vessels, and the possibility of infarction of soft tissues, particularly periosteum, are fully appreciated. It is also difficult to evaluate the effects of unequal weight bearing of the limbs. Practically all animals, however, behaved after operation much as before.

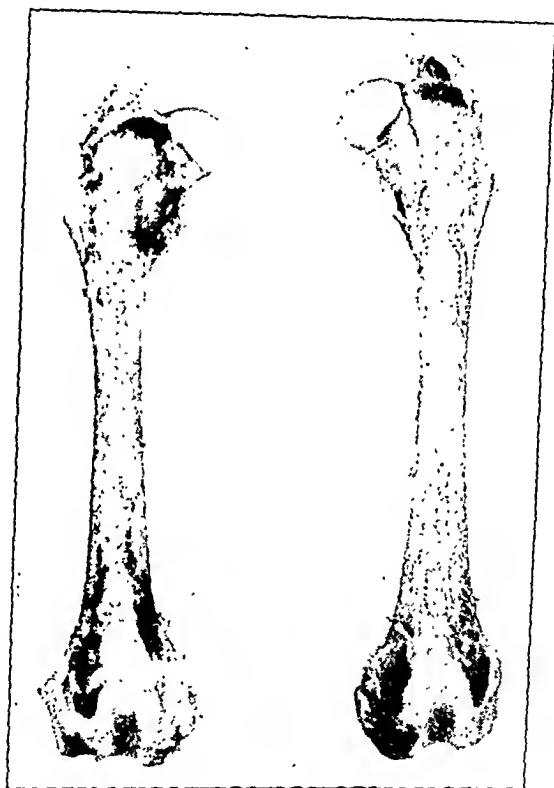


Fig. 1.—Necrosis and liquefaction of the distal epiphyseal cartilage of the right femur in a young (3 weeks) rabbit fourteen days after the injection of carbon into the nutrient artery to the shaft. The right femur is 4 mm. shorter than the left femur.

Definite gross external alterations in the size and the configuration of the femur were noted ten or more days after infarction. The cortical bone corresponding to the site of the infarcts was thickened, often porous, and its periosteal surface roughened, especially at the insertion of muscles and tendons. Other changes, present only in growing bones, were associated with the lack of continuity in the medullary circulation between the diaphysis and the epiphysis. Infarcts of the distal end of the shaft produced hypoplasia of ossification in the distal cartilage plate

amounting to as much as 4 mm. of growth in seventeen days (fig. 1), while infarcts of the proximal portion of the femur produced shortening because of interference with growth from the proximal epiphyseal line. When the head and neck were deprived of blood, the head became flat and broad so that its brim overhung the shortened neck, and the angle made by the neck and the shaft was more acute than normal (*coxa vara*), as in figure 2. There were complete necrosis and absorption of the head and neck in one growing animal examined thirty days after

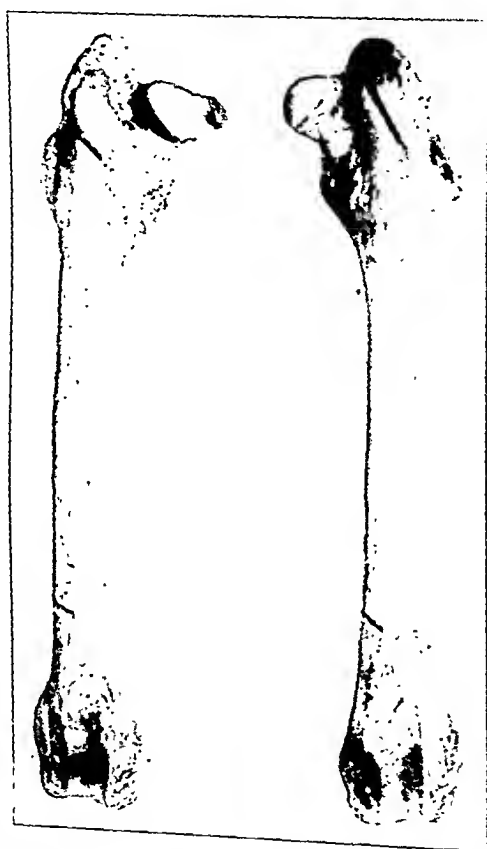


Fig. 2.—Right and left femurs of a young rabbit one hundred and fifty days after division of the right ligamentum teres and the vessel that entered the trochanteric notch. The weight-bearing surface of the head of the right bone is flattened so that the edges overhang the neck, which is shorter than the left and makes a more acute angle with the shaft. The upper portion of the shaft of the right femur is bowed laterally, and there has been less growth here than in the left.

rupture of the ligamentum teres and the vessel that entered the trochanteric notch accompanied by considerable trauma to the bone and cartilage tissues of the head. When infarction of the entire shaft was produced by particles of carbon entering all of the nutrient vessels proximal to the distal epiphysis, the shaft tended to bow laterally, and



the head and neck rotated forward as though the entire shaft were twisted.

Surfaces made by splitting the femurs longitudinally after decalcification demonstrated certain noteworthy features. Infarcts produced by emboli injected through the nutrient artery of the shaft of growing bones were proportionately larger and extended to the regional cartilage plate, while those in adult bones extended only to within from 6 to 10 mm. of the obliterated growth line. The recent infarcts were dark red and poorly differentiated, while the older ones were demarcated from adjacent vascular marrow by centers of pale gray tissue of the nature of fat that had margins of a more fibrous texture. In these infarcts, the necrosis was more marked, and the junction of living and dead tissues was more distinct distal to the level of the nutrient foramen because of the more abundant smaller accessory nutrient vessels in the proximal portion of the shaft. The delimitation by anemia and necrosis was accentuated by the intravenous injection of lithium-carminc or india ink previous to killing the animals. Such infarcts did not follow interruption of the circulation outside the cortex except in one instance in which ligation of the nutrient artery to the shaft in a rabbit 3 weeks of age produced, in nine days, a wedge-shaped infarct in the center of the distal metaphysis. The base of this anemic region was at the cartilage plate, which was twice as wide as the corresponding plate of the other femur, as if there had been marked impairment to normal ossification of cartilage (fig. 3). It is significant that during these nine days the femur which had not been operated on outgrew the femur in which infarction had been produced by 2 mm. Metaphyseal infarcts produced by the injection of carbon caused similar hypoplasia of bone, but the epiphyseal lines in these femurs closed earlier than those of the control femurs. This difference in alteration of the growth line is based on sufficient nutritional disturbance to prevent ossification by ligation of a vessel contrasted with complete infarction, even of the proliferating cartilage, produced by the embolic occlusions of vessels (fig. 4). In another young rabbit the lateral half of the head of the epiphysis was an anemic infarct four days after charcoal had been introduced into the femoral artery in such a way that a portion was carried through the vessels of the ligamentum teres. The entire head was infarcted, and there was considerable deformity of it and of the neck in a growing rabbit examined thirty days after rupture of the ligamentum teres and injection of carbon into the nutrient vessel of the shaft. Similar but less marked anemic necrosis and deformity usually followed rupture of the ligamentum teres and the vessel entering the proximal end of the femur in the trochanteric notch. In one femur subjected to this procedure there were complete necrosis and absorption of the head and a portion of the neck. To corroborate the distribution of carbon and blood



Fig. 3.—Inhibition of metaphyseal ossification and subsequent overgrowth of the distal epiphyseal cartilage plate in a femur of a young rabbit nine days after ligation of the nutrient artery to the shaft;  $\times 15$ .

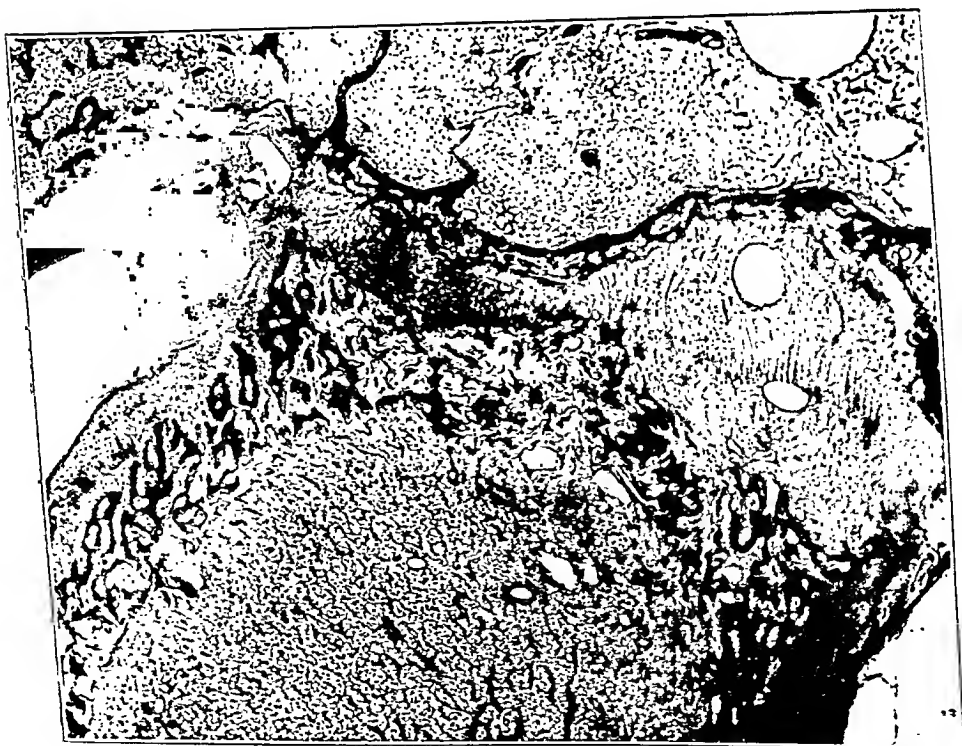


Fig. 4.—Necrosis and liquefaction of the distal epiphyseal cartilage plate in the femur of a young rabbit fourteen days after infarction by charcoal emboli;  $\times 15$ .

supply through the ligamentum teres, histologic preparations of decalcified acetabula cut longitudinally demonstrated carbon and necrosis in the bone tissues of the ischium, but not in the portion of the ilium that goes into the formation of the acetabulum.

Histologically, infarcts produced by charcoal emboli, regardless of their situation and the reaction in and about these regions of necrosis, may be considered as a group, for they differ only in extent and in local opportunity for revascularization and ultimate replacement of tissue. The following summarizing description is confined chiefly to embolic infarcts of the shaft of the femur, since they occurred regularly and were of a fairly uniform pattern. In the medullary tissues infarcted for twenty hours there were diffuse hemorrhages, mainly in the center of the medullary canal and at the junction of the infarct and neighboring normal tissues. The marrow cells stained poorly, and there was beginning disintegration of tissue, particularly about small blood vessels occluded by the carbon (fig. 5). In some there were columns of epiphyseal cartilage cells, especially on the metaphyseal side of the epiphyseal plate, that had diminished or altered staining reactions. After two days the region of necrosis was well defined by its granular nature and the absence of cellular structure, usually more prominent in the center of the cavity of the infarcted bone. Within four days there was a diminished staining reaction of the endosteal bone in the center of the infarct, and some of the lacunae were empty. The inner surface of this compact bone was irregular and without the usual layer of osteoblasts. At the junction of the necrotic and noninfarcted medullary tissues there was considerable hyperemia with a beginning sequestration, as evidenced by an increased fine fibrillar stroma. If the infarct included a metaphyseal end of the shaft, the reactive changes developed from the angle of the epiphyseal line and the cortex alone and not from the cartilage. For this reason, and because of the avascularity of articular cartilage, infarcts of the head of the femur were more or less isolated, and they produced less active regenerative changes.

Infarcts of nine days' duration (fig. 6) demonstrated a marked reparative reaction to the dead tissues. The limiting walls of the infarcts were more dense vascular fibrous connective tissue, and extending into them from the endosteum were small spicules of new bone. These partitions of the medullary cavity resembled nonspecific chronic granulation tissue, and they were cone-shaped with the tip pointed away from the infarct as though there were more destruction in the center of the cavity than along the cortical bone. This arrangement was probably due to the diagonally downward and outward branching of the central nutrient vessel in the shaft and to the greater blood supply of the marrow along the endosteum. After fourteen days the inner one fourth to

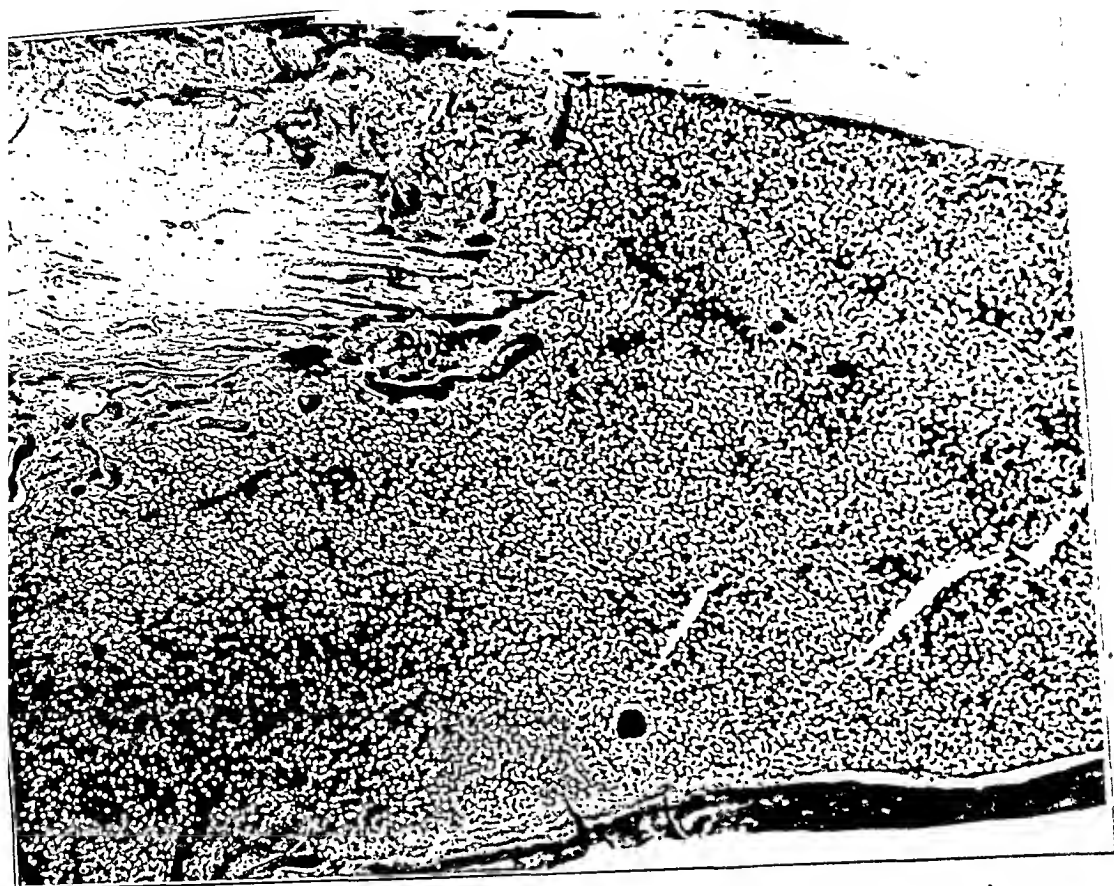


Fig. 5.—Hemorrhages and necrosis of the marrow tissues in the proximal end of a femur four days after infarction by charcoal emboli;  $\times 15$ .

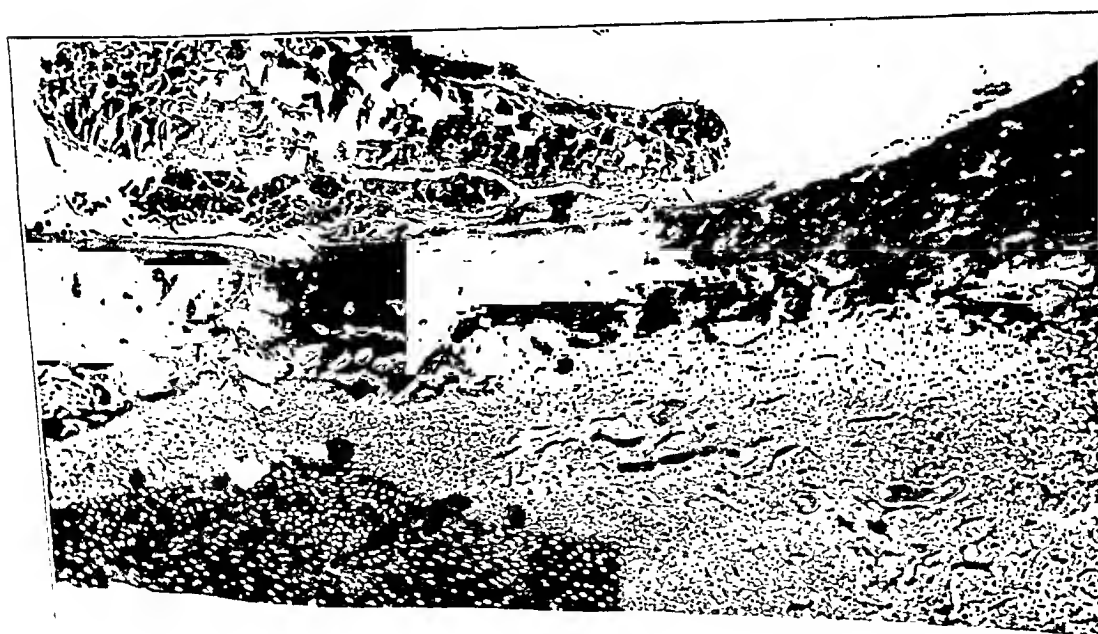


Fig. 6.—Zone of reaction with beginning proliferation of endosteal new bone and spicules of dead bone about necrotic marrow tissues nine days after infarction by charcoal;  $\times 15$ .

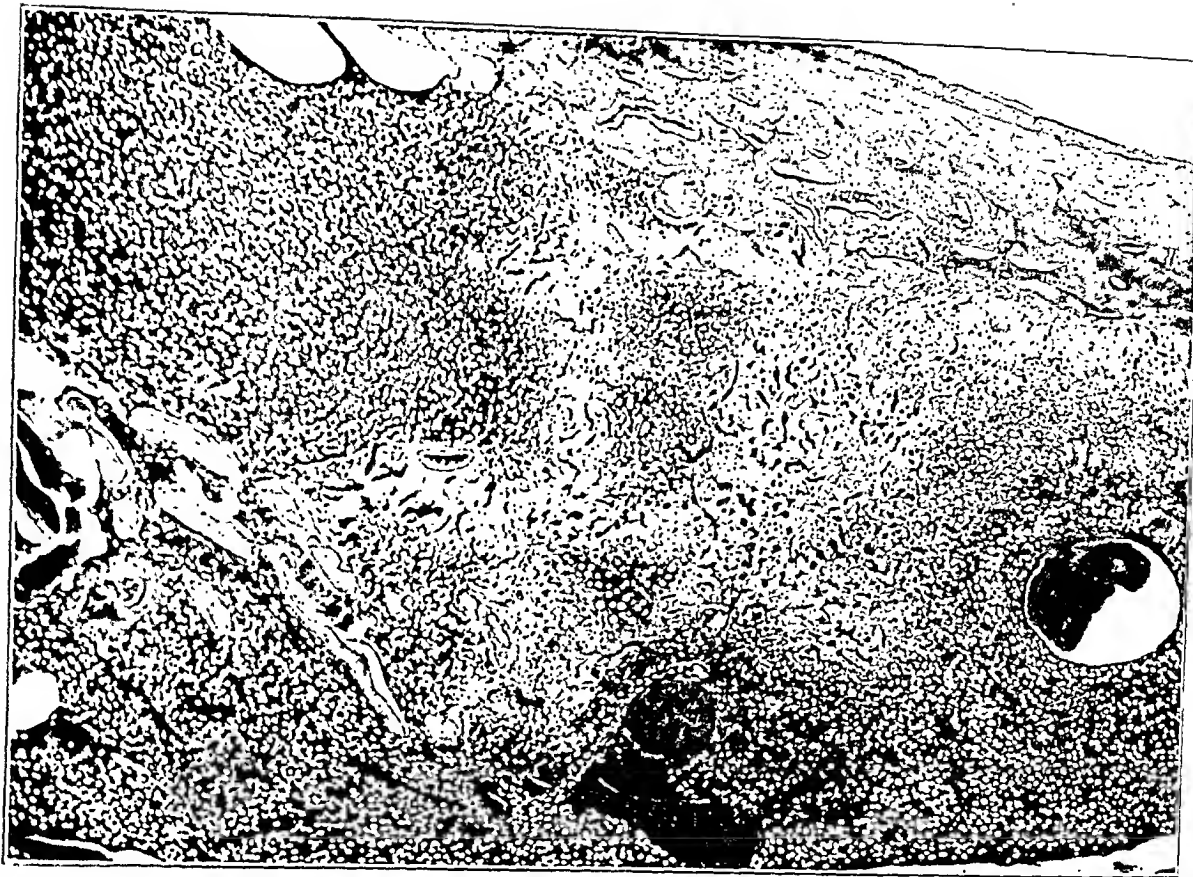


Fig. 7.—Revascularization of an infarcted region in the proximal end of the femur fourteen days after the injection of charcoal. Necrotic trabeculae and endosteal bone are being replaced by new bone. Reduced from a magnification of  $\times 15$ .

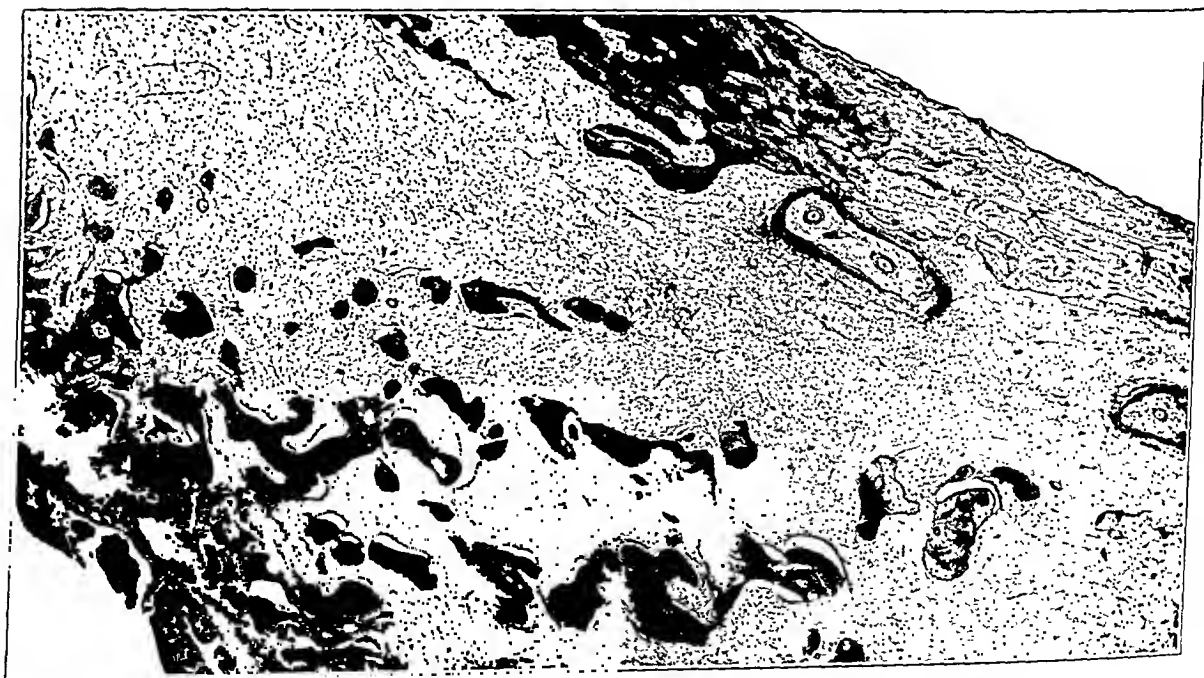


Fig. 8.—Replacement of the marrow tissues of the neck of the femur by sparsely cellular edematous fibrillar connective tissue (edema ex vacuo) twenty-seven days after division of the ligamentum teres and the nutrient vessel that pierces the cortex in the trochanteric notch. There is new bone formed about the blood vessels;  $\times 15$ .

one third of the cortical bone was definitely delimited from the outer portion by its diminished staining reaction, empty lacunae and irregular eroded inner surface (fig. 7). At the limits of the infarcts of the shaft, except beneath an epiphyseal plate, there was considerable formation of spongy endosteal and periosteal new bone. The periosteal new bone was definitely delimited from the old cortical bone and was particularly abundant at the attachments of muscles and tendons. Occasionally, new

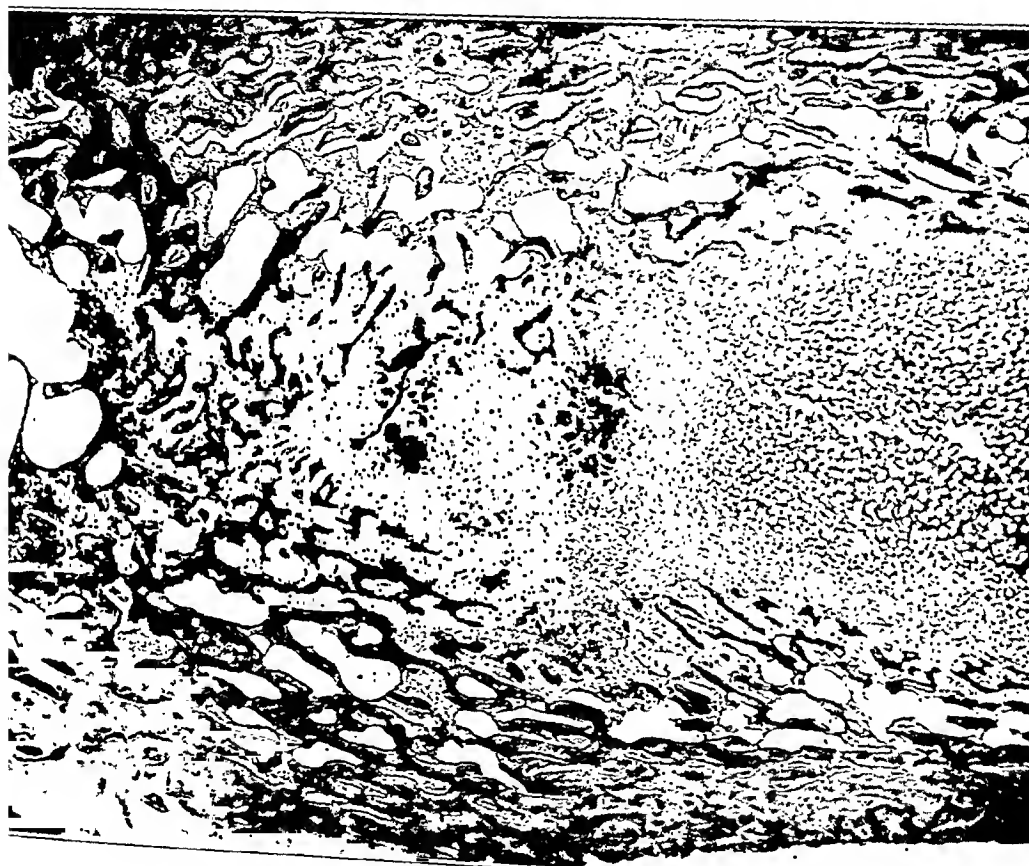


Fig. 9.—Distal end of an infarct of the shaft after forty-three days, demonstrating disseminated particles of carbon in the fibrous scar tissues, necrosis of the marrow tissues, eroded endosteum and proliferation of endosteal bone:  $\times 15$ .

bone was formed about old spicules that had been caught in the zone of reaction. The center of the infarct at this time was anemic and composed of diminished, finely granular debris in which at times a relative increase in fat and many vessels occluded by carbon were noted. These were supported in a loose, fine, fibrillar network with clear, pale blue-staining spaces between the fibrils (edema ex vacuo), as shown in figure 8. In one young rabbit, examined fourteen days after infarction of the shaft by carbon, there were complete necrosis and liquefaction



of the distal epiphyseal cartilage line. This femur was considerably shorter than the control bone of the other leg. During this and later stages there were occasional large deposits of calcium salts at the distal epiphyseal line of the infarcts of the shaft and in the bony epiphysis. One such deposit was in the cortical bone of an infarcted region.

At the height of the reaction to an anemic infarct (fig. 9), which was from forty to fifty days after injection, the limiting walls were



Fig. 10.—Septum of spongy bone through the medullary canal between necrotic and viable marrow tissues forty-three days after the injection of charcoal into the nutrient artery of the shaft of a femur. There is also formation of periosteal new bone;  $\times 15$ .

dense fibroblastic tissue with many large multinucleated cells, and some bones had osseous bridges arching across the medullary canal-like septums (fig. 10). Around some of the newly formed blood vessels of this granulation tissue were collarets of cellular fibrous tissue and spicules of new bone. The original cortex was a narrow stratum of poorly stained, eroded bone between two layers of new osseous tissue formed from the endosteum and the periosteum (fig. 11). The new

bone associated with the periosteum was particularly abundant where its blood supply was enhanced by the attachment of a muscle or tendon; that developing along the endosteum was associated with an inner layer of fibrous tissue which maintained its blood supply from the ends of the infarct or by way of small periosteal vessels that had pierced the cortex (figs. 12 and 13). There was a marked diminution of cartilage in the epiphyseal lines as compared with the controls, and in some it was entirely absent.

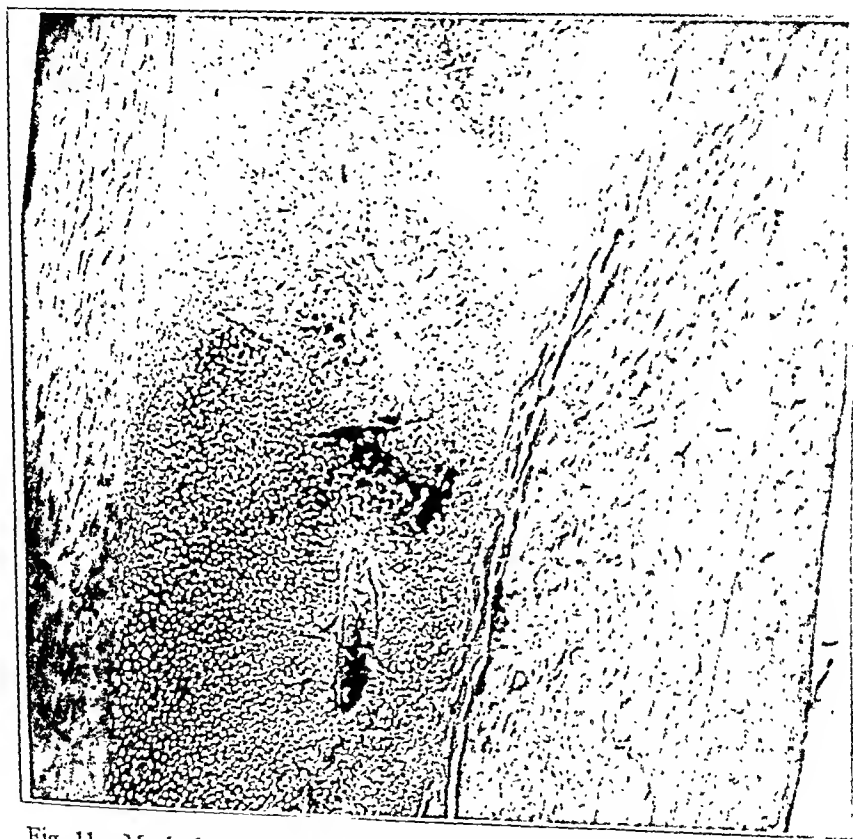


Fig. 11.—Marked proliferation of endosteal and periosteal new bone of the cortex on one side of the shaft forty-nine days after infarction with carbon emboli. There is necrosis of the inner laminae of the bone on the opposite side without replacement by new bone. A branch of the nutrient artery to the shaft is occluded by carbon;  $\times 15$ .

The ultimate fate of this reparative process was revascularization of the infarcted region, absorption of the débris and replacement of the dead cortical bone. Femurs examined three or four months after infarction by the usual procedure presented only the residue of necrosis and widely disseminated fine granules of carbon. In the medullary cavity were moderately edematous cellular tissues with many large multinucleated cells (foreign body giant cells) and blood vessels, some with





Fig. 12.—Cone-shaped fibrous tissue wall separating infarcted and viable tissues, with spicules of new bone extending from the endosteum forty-nine days after the injection of charcoal;  $\times 11$ .



Fig. 13.—Higher magnification of proliferation of endosteal new bone in the limiting zone of reaction in figure 12;  $\times 60$ .

collarets of dense fibrous tissue, in a connective tissue framework. A few small spicules of bone and masses of debris remained. At this time the original cortical bone, not yet displaced by new bone, was markedly eroded and quite distinct from the new.

Interference with the blood supply to different portions of the femur by the rupture of one or more nutrient vessels did not produce infarcts as described previously, and there was not the stimulus to promote reactionary changes. Ligation of the nutrient artery to the shaft decreased the staining reaction of medullary tissues in growing rabbits and produced slight necrosis in the metaphysis, which was of little consequence. An exception to this was the wedge-shaped metaphyseal infarct and overgrowth of epiphyseal cartilage line that occurred in a 3 week old rabbit. Division of the ligamentum teres in adult rabbits produced no change. In growing animals there was slight variable necrosis. When this procedure was combined with division of the vessel which centers the trochanteric fossa or with the injection of carbon into the nutrient artery to the shaft, the changes were marked. Interference with the vessel entering the notch alone produced only mild reactive changes localized to that portion of the proximal end of the femur.

#### COMMENT

The production of necrosis of bone by intra-arterial injection of particulate charcoal supports the belief that anemic infarction of these tissues may occur, despite their great vascularity. It also demonstrates that the vascular system of the rabbit's femur is closed, otherwise such emboli would be only foreign bodies disseminated in tissues without producing nutritional disturbance. While emboli such as these never occur in human tissues, it is fair to believe that fewer or smaller bodies acting similarly would cause proportionately less damage of the same general character. Consequently, particulate material within the vascular system of bone, by the very nature of its tissue structure, may be distributed to regions that normally have but one source of blood supply. If such particles are infectious and obstruct the circulation, a variably destructive agent is superimposed on a disturbance of nutrition.

The infarcts produced in rabbits were intimately associated with the metaphyses of growing bones. This is in accordance with the general view that the cartilage epiphyseal line is often the site of lesions of the bone considered as necroses. The difficulty encountered in producing infarcts in adult femurs and the tendency for these infarcts to be near the center of the shaft when the injection is made into the nutrient artery to the shaft emphasize the alteration in circulation that occurs when the epiphyses and the diaphysis unite. When the continuity of bone is interrupted, the severed portions can no longer depend on each other but must utilize other sources of blood supply. Should the col-

lateral circulation be inadequate, nutritional changes follow. This is the condition in so-called aseptic necrosis of the head of the femur, which occurs in adult as well as in growing femurs. In such conditions the continuity of bone is broken proximal to the entrance of epiphyseal vessels into the head from the periosteum and capsule, and the blood supply through the ligamentum teres is interrupted. Such a fragment is a segregated body, the fate of which depends on whether or not the tissues are revascularized and the necrotic bone replaced by new bone.

The bone tissues beneath articular cartilages are anatomically analogous to those situated beneath wide cartilage epiphyseal lines that are not penetrated by blood vessels. There is only a limited opportunity for the development of collateral circulation. It is reasonable to suppose that the many manifestations of subchondral necrosis may be primarily a nutritional disturbance associated with some other deleterious factor.

The infarcts produced experimentally in rabbits demonstrated absorptive reactive changes but no sequestration of dead bone. This is unlike many of the clinical entities embodying necrosis in which an impairment of circulation has occurred. Such differences may depend on the nature of the emboli or the trauma to which these regions of bone are subjected. By trauma in this sense is meant not severe sudden injury, but the trauma of friction, such as between component parts of a bone that are not equally capable of bearing a given stress. In other words, there is a break in the uniformly rigid character of the bone. Since weight bearing is the greatest stress placed on bones, such secondary changes probably would occur in bones of the legs and feet, particularly in the parts subjected to the maximum load. The added insult of weight trauma to such a focus may be sufficient not only to impair the healing but also to increase the lesion to the extent that a fragment of bone is entirely loosened from its bed, as in König's osteochondritis dissecans of the internal condyle of the femur (separating process of Axhausen). Compression fracture of bone trabeculae and their pulverization to bone detritus with hemorrhages often are present. There is no way of determining how frequently unrecognized focal necrosis of bone occurs, the so-called silent foci. An adequate reparative process is dependent probably on sufficient nourishment.

A disturbance in normal nutrition to an epiphyseal cartilage of a long bone interferes with growth. If there is diminished blood supply to a metaphysis, proliferation of cartilage may continue without ossification, while infarction of a cartilage plate produces necrosis. The endosteum and periosteum both react to a disturbance of nourishment to cortical bone by the production of new in the place of old bone. This proliferation of bone in the infarcts of the femurs was particularly active about the blood vessels at the junction of the viable and the necrotic

tissues. The deposition of inorganic calcium salts in infarcts of bone is probably calcification of necrotic tissues that already have a high content of this element.

#### SUMMARY

Infarcts were produced in the femur of young and adult rabbits by intra-arterial injection of a particulate suspension of charcoal and by interruption of one or more nutrient vessels outside the cortex of this bone.

The necrosis and reactive changes that occurred in from twenty hours to one hundred and fifty days after infarction have been described and correlated with a discussion of the more common clinical entities that concern necrosis in bone.

# APPENDICITIS AND ACUTE INFLAMMATORY ABDOMINAL CONDITIONS IN SCARLET FEVER

REPORTS OF NINE CASES AND REVIEW OF THE LITERATURE

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This article deals with appendicitis and similar acute inflammatory abdominal conditions as they occur in scarlet fever. It was prompted by the fact that these conditions were seen repeatedly in patients with scarlet fever admitted to the Durand Hospital. The histories of these cases, a review of cases found in the literature available, and comments on the incidence, pathogenesis, morbid anatomic characters, clinical aspects and treatment are presented.

These abdominal disorders, principally of the right lower quadrant and particularly appendicitis, have been seen in the various exanthems, in anginal disorders and in disease of the respiratory tract and lungs. They have been observed in measles, mumps, whooping cough, chicken-pox, smallpox and typhus.<sup>1</sup> During widespread disease of the upper respiratory tract and in pulmonary and influenzal conditions, appendicitis has been noted in almost epidemic proportions.<sup>2</sup> Appendicitis has followed inflammatory tonsillar disease<sup>3</sup> and rheumatic fever.<sup>4</sup>

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From the Durand Hospital of the John McCormick Institute for Infectious Diseases, Chicago.

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(Footnotes continued on next page)

While there is no good reason for delimiting the occurrences to scarlet fever alone, it is the impression that they appear more frequently and in more unique situations in this exanthem. Certainly from a review of the cases in the Durand Hospital and of those in the literature it appears that the association of appendicitis and other inflammatory states with scarlet fever should be emphasized more than it has been.

Generalized, primary or idiopathic peritonitis in scarlet fever<sup>5</sup> is not included in the discussion.

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The following cases are reported from the Durand Hospital.

#### REPORT OF CASES

CASE 1.—H. N., a girl, aged 9 years, was admitted on April 22, 1913. On April 18 she had become suddenly ill with headache, malaise, chills, vomiting and a rash. Examination showed pallor about the lips, a tongue with large papillae, enlarged and reddened tonsils, enlargement of the lymph nodes in the neck, groin and axillae and a generalized scarlatiniform rash. The temperature ranged between 100 and 102 F. The white cell count was 10,000. On April 23 pain appeared in the right knee and wrists; it disappeared two days later. The temperature at that time varied between 100 and 101 F. Late on April 26 and through the following day pain in the right side of the abdomen and vomiting were present. The temperature ranged between 100.4 and 103 F. There were increased resistance and tenderness to palpation over McBurney's point. The white cell count was 31,000. Between April 27 and 29 the pain subsided. The temperature was normal on May 3.

CASE 2.—C. M., a boy, aged 15 years, was admitted on Aug. 25, 1913. He had been operated on for appendicitis at another hospital and was admitted because of a rash following operation. Examination revealed a brilliant scarlet rash over the abdomen and chest, enlargement of the lymph nodes of the neck, groin and pectoral region and a recent draining appendectomy wound. The temperature varied between 98 and 100.4 F. during the first five days and was normal thereafter. The white cell count was 10,000. Hemolytic streptococci were cultured from the throat. The rash faded about twenty-four hours after admission. At the end of five days the patient was returned to the first hospital. Details of the illness prior to the appendectomy and of the condition of the excised appendix were not obtained.

CASE 3.—D. P., a girl, aged 10 years, was admitted on May 11, 1914. She had had a diarrhea of one month's duration. On May 7, 8, 9 and 10 she suffered from dizziness, headaches, sore throat, increasing pain in the lower part of the abdomen, nausea and vomiting, fever and diarrhea. Examination disclosed an acutely ill child with a purulent nasal discharge, herpes of the lip, pallor about the lips, enlargement of the lymph nodes of the neck and a scarlet and punctate eruption. The abdomen was diffusely tender; the right lower quadrant was more tender and resistant to touch. There was a gonorrheal vaginitis. The white cell count was 16,000. Hemolytic streptococci were cultured from the throat. The temperature varied between 102 and 104 F. On May 12 the pain was definitely localized at McBurney's point and persisted so until May 14. On May 20 there was transitory pain in the ears.

CASE 4.—F. DeH., a woman, aged 21, was admitted on March 8, 1915. Four days previously she had become suddenly ill, with a loss of appetite, sore throat, constipation and a rash three days later. The temperature was elevated. On inspection, there were enlargement of the lymph nodes of the neck and of the papillae of the tongue, reddening of the pharynx, reddening and enlargement of the tonsils, pallor about the lips and a generalized and punctate red rash. The temperature averaged 98.5 F., with an occasional rise to 100 F. The white cell count was 8,100; in the differential smear there was a slight increase in eosinophils. On March 15 she complained of pain and tenderness in the right lower part of the abdomen. There was no muscular resistance. On March 16 the white cell count was 8,400. The pain disappeared on March 19.

CASE 5.—M. L., a nurse, aged 22, was admitted on May 28, 1917. Illness had developed suddenly on May 25. The patient complained of nausea and sore throat. A rash appeared on the day of admission. On examination the patient appeared

prostrated. Other signs were enlarged lymph nodes of the neck, a "raspberry tongue" and a confluent and red macular rash. On May 27 the white cell count was 16,000. The temperature varied irregularly from 99 to 101 F. and averaged 100 F. up to June 3. The rash and other symptoms and signs disappeared on June 4. There was profuse peeling of skin on June 6. Until June 21 the patient complained of nausea and pain in the right lower part of the abdomen. The abdomen was tender and resistant to pressure over McBurney's point. Successive white cell counts were 9,400, 10,600 and 12,300, with increasing numbers of polymorphonuclears. The temperature became normal. In consideration of the pain, tenderness and resistance of the abdomen and the increasing number of white blood cells appendectomy was considered, advised and refused.

CASE 6.—S. P., a girl, aged 5 years, was admitted on Nov. 24, 1917. In the past she had had "chronic appendicitis." On November 19 the appendix had been removed at another hospital. It was stated that the appendix was 9 inches (22.8 cm.) long, generally reddened at the distal 2 inches (5 cm.) and adherent to the mesentery. The temperature immediately following operation was 105. F. Cough was present on November 20 and a rash on November 22. Examination immediately after admission showed a moderately ill person. There were a "raspberry tongue" with ulcers, enlarged and reddened tonsils, a reddened pharynx, readily palpable lymph nodes of the neck and groin and a fine red macular rash with subcuticular flushing. The temperature varied between 99 and 100 F. On admission the white cell count was 11,900; on November 28 it was 18,200. The stitches sloughed out of the operative wound, and there was much foul-smelling pus. On December 6, the temperature ranged between 99.4 and 102 F. and the white cell count was 20,000. On December 8 there was a soft and boggy swelling behind the right ear; this gradually disappeared completely. The temperature was normal on December 9 and thereafter.

CASE 7.—R. M., a boy, aged 9 years, was admitted on July 24, 1919. His illness began on July 22 with itching, cutaneous eruption and vomiting. On examination the tongue was seen to be slightly reddened with accentuated papillae; the throat was reddened; the tonsils were reddened and enlarged, and the lymph nodes under the left side of the mandible were readily palpable. The rash had faded. The white cell count was 15,200. The temperature ranged between 99 and 100.4 F. The illness had the usual course until August 25, when the temperature rose to 100.8 F. and the patient complained of abdominal pain and vomited. There was no muscular resistance or tenderness. The condition lasted one day, and thereafter no untoward symptoms occurred.

CASE 8.—R. P., a boy, aged 15 years, was admitted on March 29, 1926. On March 27 the patient had been operated on for appendicitis at another hospital. The history prior to the operation had been that on the day before operation he complained of sore throat and vomited. There were no details regarding abdominal symptoms and signs. Two days after operation, a rash appeared on the body. A diagnosis of scarlet fever was made. Examination immediately after admission revealed pallor about the mouth, hyperemia of the throat and tonsils, coating of the tongue and accentuation of its papillae, moderate enlargement of the upper lymph nodes of the neck and a fading red-brown rash on the neck, axillae and abdomen. There was a recent appendectomy wound. The white cell count was 12,600. The temperature oscillated between 99 and 101.6 F. until May 4 when it was normal.

CASE 9 (personally observed).—O. E. W., a girl, aged 10 years, was admitted on Dec. 31, 1930. About two months prior to admission a moderately severe diabetes mellitus was discovered and had been treated adequately with an



TABLE 1.—Cases in Which Appendicitis Was Definitely Proved by Operation or Postmortem Examination

Case	Author, Reference	Sex, Age	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
1	Stedman, C. E.: Boston M. & S. J. 9: 756 (Dec. 28) 1876	M, 21	Dysphagia, chills, sore throat, rash on 2d day	Severe and colicky pains at umbilicus on 5th and 6th days; collapse and death	Appendix large, dilated and containing fecolith; perforation, surrounded by purulent peritonitis and adhesions	None
2	Chevassu: Arch. de méd. et pharm. mil. 28: 36, 1896	M, 21	Diagnosis of scarlet fever, nothing unusual until 14th day	On 14th day abdominal pain, fever, vomiting, weak pulse and prostration; abdominal wall resistant; operation with excision of appendix; recovery	Operation: free pus, fibrinous adhesions about cecum; appendix inflamed and perforated	None
3	Julie, M. H.: Arch. de méd. et pharm. mil. 31: 424 (June) 1898	M, ?	Diagnosis of scarlet fever, death 27 hours after onset	Vomiting; no details of abdominal pain	Intense hyperemia of abdominal viscera and volvulus of bowel; appendix long, folded on itself, containing pus and fecolith	None
4	Kelly, H. A.; and Hurdon, E.: The Vermiform Appendix, Philadelphia, W. B. Saunders Company, 1905, p. 381	M, 8	Diagnosis of scarlet fever	Diagnosis of appendicitis in 3d week; excision of appendix; recovery	No details about appendix	Cervical lymphadenitis in 3d week
5	Veuau, V.: Bull. Soc. de pédiat. de Paris 9: 361 (Dec. 17) 1907	M, 12	Diagnosis of scarlet fever	On 3d day abdominal pain, fever and vomiting; appendectomy; recovery	Operation: appendix perforated, bound with adhesions and embedded in free pus	None
6	Veuau, V., <i>ibid.</i> .....	M, 14	Diagnosis of scarlet fever	No details of abdominal distress; operation with excision of appendix; recovery	Operation: appendix enlarged and pelvic abscess	Polyarthrits
7	Veuau, V., <i>ibid.</i> .....	M, 8	Diagnosis of scarlet fever	No details; laparotomy with recovery	Abscess in right iliac fossa	Albuminuria and edema
8	David, cited by R. Kaufmann, Thèse de Paris, 1908 (see case reports of this author)	F, 6	Scarlet fever, gangrenous pharyngotonsillitis	Abdominal pain and muscular resistance in right lower quadrant; death	Appendix acutely inflamed and bound by adhesions	None
9	Routier, cited by Kaufmann....	M, 10	Diagnosis of scarlet fever	Appearance of abdominal pain 2½ weeks after onset; excision of appendix 8 weeks later	Meso-appendix inflamed; appendix oedematous and adherent to nearby bowel	None
10	Routier, <i>ibid.</i> .....	M, 17	Rash appeared 2 hours after diagnosis of appendicitis was made	Appendectomy on diagnosis of appendicitis; recovery	Appendix acutely inflamed and adherent to mesentery	None
11	Jalagulier, cited by Kaufmann	M, 15	Fever, vomiting and rash on 4th day after onset	Abdominal pain on 4th day with vomiting and elevated temperature, 7 weeks later appendectomy with recovery	Appendix ulcerated, embedded in adhesions and containing pus; meso-appendical lymph nodes enlarged	None
12	Gulman and Lefèvre, cited by Kaufmann	F. Inf.	Diagnosis of scarlet fever	Abdominal pain, vomiting and tenderness over McBurney's point; appendectomy with recovery	Acutely inflamed appendix with peritonitis	None

[illegible]

TABLE 1.—Cases in Which Appendicitis Was Definitely Proved by Operation or Postmortem Examination—Continued

Case	Author, Reference	Sex, Age	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
31	Therebe, O. L., <i>ibid.</i> .....	M, 17	Sore throat, nausea and rash	Abdominal pain and tenderness over McBurney's point; appendectomy and recovery	Operation: appendectomy, acute inflammation	None
32	Therebe, O. L., <i>ibid.</i> .....	F, 18	Sore throat, malaise and rash on 2d day	Abdominal pain and local tenderness; appendectomy with recovery 33 days later	Chronically inflamed appendix found at operation	None
33	Therebe, O. L., <i>ibid.</i> .....	M, 17	Sore throat, fever, malaise and rash	On 1st and 2d days pain in abdomen, localizing to right lower quadrant with tenderness; rash on 3d day; abdomen distended; on 4th day operation with recovery	Gangrenous appendix adherent to cecum; cecum edematous; fecal fistula as postoperative complication	None
34	D. H. series,* case 8.....	M, 15	Diagnosis of appendicitis; rash and sore throat noted; operation; vomiting; rash 2 days after operation; diagnosis of typical scarlet fever; fever, leukocytosis	No details	No details	None
35	Frank, H.: <i>Deutsches Arch. f. klin. Med.</i> 164: 159 (July) 1923	M, 11	Diagnosis of scarlet fever	On 4th day, abdominal pain and fever, on 5th, tenderness in upper part of abdomen, on 6th, distention of abdomen; laparotomy performed followed by death from general peritonitis	Operation: watery exudate in abdominal cavity, appendix 13 cm. long, retrocecal, tip touching liver; hemolytic streptococci from appendix and from peritoneal exudate after death	Otitis media
36	Bodenheimer, J. M., and Fleming, F. J.: <i>New Orleans M. &amp; S. J.</i> 81: 136 (Aug.) 1928	M, 16	Diagnosis of scarlet fever	Symptoms of appendicitis on 2d day; operation and recovery	At operation: acute appendicitis	None
37	Kelsig, E.: <i>Monatsehr. f. Kinderh.</i> 49: 389, 1921	M, 7	Abdominal pain for 1 year preceding; diagnosis of scarlet fever	Abdominal pain, tenderness and resistance of right lower quadrant; operation immediately and 32 days later; recovery	First operation, pus in lower part of abdomen but no appendix seen; second operation, appendix perforated and containing a fecalith	None
38	Finkelstein, quoted by Kalsig	?	Diagnosis of scarlet fever	Diagnosis of renal retention; laparotomy; death	Operation: perforated appendix situated behind bladder in abscess	Nephritis?
39	D. H. series,* case 9.....	F, 10	Sore throat, fever and pain in chest at onset, pallor about lips, red throat, enlarged lymph nodes in neck, and rash; antitoxin given on admission, followed in 5 days by pain in chest, enlarged lymph nodes in pectoral region, urticaria, vomiting and abdominal pain, diabetic acidosis; receded; well until 10th day	On 10th day increasing abdominal pain, vomiting, tenderness and spasticity of abdominal wall; increasing leukocytosis; operation with removal of appendix; recovery	Operation: appendix generally hyperemic and enlarged; gangrenous at tip; pelvic abscess	Diabetes mellitus; serum sickness

\* Durand Hospital series.

adjusted diet and insulin. The patient became ill rather suddenly with a sore throat, fever and a vague pain in the chest. On examination, there were found a coated tongue with enlarged papillae, pallor about the lips, a red stippled palate, large and hyperemic tonsils, many shotlike lymph nodes in the upper triangles of the neck, a bright red and diffuse fine papular rash of the trunk and large and deep red lines in the creases of the elbows. The temperature varied between 98 and 100 F. The tests for reducing substance and ketone bodies in the urine were strongly positive. On a regulated diet of milk and cream and an increase in the dosage of insulin, the urine became normal. The white cell count was 19,500. Hemolytic streptococci were cultured from the throat. Three hundred thousand units of scarlet fever antitoxin was injected intramuscularly on admission. The temperature was normal from January 3 to January 5. The rash disappeared on January 4, and there was some peeling of skin on the chest and abdomen about the same time. On January 5 pain appeared in the left axilla with probably coincident enlargement of the lymph nodes of that region as well as of those along the pectoralis muscle on the same side and the upper triangles of the neck. The next day the temperature rose rapidly to 104.6 F., dropped to 99.6 F. on the day following and then rose again to 103.6 F. On January 5 and 6 there was severe, generalized and distressing urticaria. On the two following days headache, nausea and vomiting, abdominal pain and swelling of the eyelids appeared. The vomiting was so troublesome that all feeding by mouth was discontinued and resort made to retention and nutrient enemas. Reducing substance, ketone bodies, protein and casts were abundant in the urine. On January 9 the patient was comfortable and able to take food by mouth.

Late on January 10 and throughout the following two days the abdominal pain returned with rapid and increasing severity. There were much nausea and vomiting. The temperature averaged 99.6 F. On January 11 the abdominal wall was generally and exceedingly tender and resistant to palpation. The temperature rose in abrupt steps from 98 to 102.4 F. The distress was great enough to require morphine. On January 12 and 13 the white cell counts were 26,600 and 25,000, respectively.

Diagnoses of acute mesenteric lymphadenitis, pyelitis, pleuritis and pneumonia were considered. Because of the increasingly critical condition of the patient, a laparotomy was decided on. On January 13 Dr. E. M. Miller performed the operation. An appendix with an abscess at its tip was found. The appendix itself was markedly enlarged, generally hyperemic and gangrenous and perforated in its distal portion. Hemolytic streptococci were cultured from the wall and from the pus.

The first five days after operation were difficult and complicated by "gas pains." The temperature fluctuated between 98.6 and 102 F. The diabetic condition was readily managed. The patient recovered completely.

Attention is directed to a presentation of all the cases that could be found in the literature consulted. These are presented in tabular form and the various salient features of each case outlined. The cases are tabulated in three different groups: (1) those in which appendicitis was definitely proved by operation or postmortem examination; (2) those in which some abdominal organ other than the appendix was involved as proved by operation or postmortem examination; (3) those in which only the clinical aspects are known. In these it will never be definitely known whether the appendix or another organ was involved; therefore, such cases may be considered doubtful.

Each case is presented in numerical order according to the time of publication and analyzed according to:

- Author
- Age and sex
- General clinical picture
- Specific clinical picture of the abdominal disorder
- Findings at operation or at postmortem examination
- Presence of complications or of associated disease

The cases observed at the Durand Hospital are included for the sake of completeness.

TABLE 2.—Cases in Which Some Abdominal Organ Other Than the Appendix Was Involved

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
40	Nason, E. N., and Nason, W. S.: <i>Brit. M. J.</i> 1: 908 (April 30) 1892	M, 7	Diagnosis of scarlet fever; several other members in family of patient died of malignant scarlet fever	Vomiting, abdominal pain and muscular resistance, death	Prominence and injection of Peyer's patches, enlargement of mesenteric lymph nodes	None
41	Rolly, F., in Mohr, L., and Stiehl, R.: <i>Handbuch der inneren Medizin, Berlin, Julius Springer, 1923, vol. 1, p. 85</i>	?	Diagnosis of scarlet fever	Death	Ruptured suppurating mesenteric lymph node and general peritonitis	None
42	Lewis, D.: personal communication to author	?	Diagnosis of scarlet fever	Abdominal pain, operation for appendicitis, recovery	Operation: lymph nodes between cecum and ileum inflamed, appendix normal	None
43	Lewis, D., <i>ibid.</i>	?	Scarlet fever	Abdominal pain, laparotomy, recovery	Operation: ileum diffusely inflamed for 3 feet (91 cm.), felt like "rubber hose"	None

In addition to the cases listed Gromski<sup>6</sup> reported two of abscess of the spleen, and Schlossmann and Meyer<sup>7</sup> stated that cholecystitis may occur.

The remainder of the article deals with comments on the incidence, pathogenesis, morbid anatomic changes and clinical and therapeutic aspects.

6. Gromski, M.: Two Cases of Splenic Abscess in the Course of Scarlet Fever, *Przegląd pedyatryczny*, 1912; abstr., *Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb.* 2:695, 1912.

7. (a) Schlossmann, A., and Meyer, S.: Scharlach, in Pfandler, M., and Schlossmann, A.: *Handbuch der Kinderheilkunde*, ed. 3, Leipzig, F. C. W. Vogel, 1923, vol. 2, p. 131. (b) Delage, J.: *Bull. Soc. de pédiat. de Paris* 30:249 (April) 1932. (c) Saxl, O., and Gross, F.: *Med. Klin.* 28:1168 (Aug.) 1932.

TABLE 3.—Cases in Which the Exact Condition Was Not Ascertained

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Complication or Associated Disease
44	Sutton, A. M.: <i>Lancet</i> 2: 1155 (Oct. 25) 1899	?	Angina and rash, diagnosis of scarlet fever	On 4th day, abdominal pain and vomiting, tumor felt in right lumbar region, recovery	None
45-49	Simonin: <i>Bull. et mém. Soc. méd. d. hôp. de Paris</i> 18: 1358 (Dec. 27) 1901	M, 21 to 24	Diagnosis of scarlet fever	Abdominal pain, nausea and vomiting, tenderness over McBurney's point, spontaneous recovery, usually diagnosed "latent catarrhal appendicitis"	Joint, muscular and possibly hepatic disorders
50-53	Bardon, C.: <i>Quelques mots sur le rôle étiologique des maladies infectieuses dans l'appendicite</i> , Thèse de Paris, Masson & Cie, 1914, p. 166	?	Usually severe angina, jaundice	Tenderness deep in right lower abdominal quadrant on 3d to 17th day, usually diagnosed appendicitis, recovery	None
54	St. Paul, cited by Kauffmann, Thèse de Paris, 1908.	?, 2½	Diagnosis of scarlet fever	Abdominal pain, death	None
55	St. Paul, <i>ibid.</i>	?, 7½	Scarlet fever with marked intoxication	Abdominal pain, death (in foregoing 2 cases no postmortem examination)	None
56	St. Paul, <i>ibid.</i>	M, 11	Diagnosis of scarlet fever	Abdominal pain, recurred in 6 months	Nephritis
57	Marfan, cited by Kauffmann	M, 10	Diagnosis of scarlet fever	Abdominal pain	None
58-60	Kauffmann, R.	8½ to 11½	Diagnosis of scarlet fever	Abdominal pain and local tenderness 1 to 2 days after onset, recovery	None
61	Escherich and Schiek, cited by Seitz (case 24)	F, 12	Diagnosis of scarlet fever	Early in disease, palpable tumor in right lower quadrant, tenderness over McBurney's point	None
62	Escherich and Schiek, <i>ibid.</i>	?	Diagnosis of scarlet fever	Acute appendicitis during convalescence, no operation	None
63	Meyer, O.: <i>Berl. klin. Wchnschr.</i> 11: 455, 1913	M, 4	Diagnosis of scarlet fever	Pain in abdomen and neck, vomiting, tenderness and muscular spasticity over McBurney's point, recovery, followed by 2 subsequent exacerbations	None
64	Meyer, O., <i>ibid.</i>	M, 11	Chill, fever, rash and swollen and hyperemic throat	On 2d and 3d days abdominal pain	Suppurative inguinal lymphadenitis
65	D. H. series,* case 1	F, 9	Headache, chills, vomiting, rash, hyperemic pharynx, enlargement of lymph nodes in neck, groin and axilla; fever and leukocytosis; recovery	On 4th day, abdominal pain with increased severity in lower right abdominal quadrant, vomiting and fever, tenderness over McBurney's point, much increased leukocytosis, regression on 6th day	Pain in right knee and wrists on 2d day, disappeared
66	D. H. series,* case 3	F, 10	Diarrhea for 1 month; headache, sore throat, rash and enlargement of lymph nodes; leukocytosis; hemolytic streptococci cultured from throat; recovery	Abdominal pain, nausea and vomiting near onset, tenderness in right lower quadrant, fever, pain definitely over McBurney's point on 2d day, gone by 4th day	Purulent rhinitis, gonorrheal vaginitis, otitis?

\* Dursand Hospital series.

## INCIDENCE

There is too little information at hand to permit any statement as to the frequency of occurrence of appendicitis and the other abdominal disorders in scarlet fever. A number of textbooks on infectious diseases, pediatrics, internal medicine and surgery do not mention the subject. Rolleston<sup>8</sup> stated that appendicitis may occur in scarlet fever but that he never saw a case. Heubner,<sup>9</sup> Jochmann<sup>10</sup> and Schlossmann and Meyer<sup>7a</sup> believe that it is not at all uncommon. Pospischill and Weiss<sup>11</sup> saw one patient with appendicitis in their clinical experience. Caiger<sup>12</sup>

TABLE 3.—Cases in Which the Exact Condition Was Not Ascertained—Continued

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Complication or Associated Disease
67	D. H. series,* case 4	F, 21	Sore throat, malaise; rash on 3d day; lymph nodes of neck enlarged; slight eosinophilia; recovery	On 7th day, pain and tenderness in right lower quadrant, no leukocytosis, symptoms disappeared on 8th day	Nonspecific vaginitis
68	D. H. series,* case 5	F, 22	Sudden onset; sore throat, fever; rash on 3d day; enlargement of lymph nodes of neck; leukocytosis; recovery	On 24th day, pain in right lower quadrant with nausea and vomiting, tenderness in right lower quadrant, increasing leukocytosis, appendectomy recommended and refused	None
69	D. H. series,* case 7	M, 9	Eruption of skin, vomiting; pharynx hyperemic; lymph nodes about and under left ear enlarged; recovery	On 34th day, vomiting and abdominal pain for 1 day	None
70-73	Finklestein, quoted by Kalsig (case 37)	?	Diagnosis of scarlet fever	Diagnosis of appendicitis during course	None

\* Durand Hospital series.

did not refer to any possible occurrence of these diseases in his report of one thousand and eight cases of scarlet fever. Table 4 may give some, but very likely poor, conception of the relative frequency.

8. Rolleston, J. D.: *Acute Infectious Diseases*, London, William Heinemann, Ltd., 1929, p. 274.

9. Heubner, O.: *Lehrbuch der Kinderheilkunde*, Leipzig, Johann Ambrosius Barth, 1906, vol. 1, p. 383.

10. Jochmann, G.: *Lehrbuch der Infektionskrankheiten*, Berlin, Julius Springer, 1924, p. 669.

11. Pospischill, D., and Weiss, F.: *Ueber Scharlach (der Scharlacherkrankung, zweiter Teil)*, Berlin, S. Karger, 1911, p. 89.

12. Caiger, F. F.: *An Analysis of 1,008 Cases of Scarlet Fever Admitted into the Southwestern Fever Hospital During the Year 1890*, *Lancet* 1:1249 and 1304 (June 6 and 13) 1891.

By further and more exhaustive studies it may be demonstrated that appendicitis and the other abdominal conditions occur much more often than indicated; I believe this to be true.

#### PATHOGENESIS

The pathogenesis of appendicitis and of the other conditions in scarlet fever is known only in general.

A common and much held view is that these conditions, at least appendicitis, are hematogenous metastatic products of which the hemolytic streptococcus, among others, is the cause and the pharynx the source of dissemination. No attempt will be made to dwell in any detail on this exceedingly controverted view, except to point out its numerous discussions as seen in the articles of Brenneman,<sup>2d</sup> Kaufmann,<sup>13</sup> Aschoff<sup>14</sup> and Christeller and Mayer.<sup>15</sup>

It is of interest to state the theory of Kretz,<sup>16</sup> who is a strong advocate of the hematogenous origin of appendicitis. According to him, the organism is conveyed by the blood stream to the lymphoid follicles and

TABLE 4.—Frequency of Appendicitis in Scarlet Fever

Source	Cases of Scarlet Fever	Cases of Appendicitis
Durand Hordtke	4,563	0
Richter	4,523	8
Thien	250	4

their constituent capillaries. There the capillaries are destroyed, organisms liberated into the tissue spaces and variously acute exudative, proliferative and resolving inflammatory reactions incited. As an evidence of capillary damage emphasis is placed on the presence of submucosal hemorrhages. Aschoff denies any significance to these hemorrhages.

McMeans<sup>17</sup> gave an excellent review of the difficulties encountered in investigating the theory that appendicitis originates through the blood stream.

13. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co. 1929, vol. 2, p. 835.

14. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908, p. 85; Pathogenese und Aetiologie der Appendizitis, *Ergebn. d. inn. Med. u. Kinderh.* 9:1, 1912; Zur Pathogenese und Aetiologie der Appendizitis, *München. med. Wehnschr.* 54:1152 (June 4) 1907.

15. Christeller, E., and Mayer, E.: Appendizitis, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, p. 3, p. 469.

16. Kretz, R.: Angina und septische Infektion, *Ztschr. f. Heilk.* 27:296, 1907; Studies upon the Etiology of Appendicitis, *Internat. Clin.* 1908, series 18, p. 285.

17. McMeans, J. W.: Experimental Appendicitis, *Arch. Int. Med.* 19:709 (May) 1917.



Other theories may be briefly mentioned. Some believe that the organisms are swallowed and implanted in the interior of the organ affected. It has been suggested that there is a catarrh of the adjacent portion of the bowel which extends to the appendix. The fecalith may be important as a nidus of infection.

It is important to realize that the appendix is not invariably involved in the lesions which attract attention to the right lower quadrant of the abdomen. From the reports it may be seen that the ileocecal lymph nodes, probably the lymphoid tissue of the ileum, possibly mesenteric lymph nodes elsewhere and even the spleen may be involved in scarlet fever. Each of these may cause symptoms and signs so similar to those of appendicitis as to make a differential diagnosis difficult or impossible.

The whole lymphoid apparatus<sup>18</sup> is involved in the onset and course of scarlet fever. This may be inferred, for example, from the enlargement of the lymph nodes in the neck, groin and elsewhere as seen in routine examination. The reactions in these sites may regress or show further change in a small sphere, as, for example, in the neck. They may go on to more pronounced inflammation, to suppuration and to necrosis. The same reactions may exist in the appendix and other abdominal aggregates of lymphoid tissue so that the condition may occur in one of two ways: (1) as a part of the general reaction of the lymphoid apparatus at the onset and figuring in the production of abdominal symptoms of the prodrome of scarlet fever; (2) as one or several lymphoid aggregates that may go on to an acute abdominal lymphadenitis in the appendix, ileocecal mesentery and ileum and elsewhere.

#### MORBID ANATOMIC CHANGES

The abdominal organs that may be involved are: (1) the appendix (preponderantly); (2) the lymph nodes between the ileum and cecum with or without coincident appendicitis; (3) the lymphoid patches of the ileum; (4) possibly the lymphoid tissue of the cecum itself; (5) the lymph nodes elsewhere in the mesentery, and (6) the spleen.

The "typhlitis" and "epityphlitis" of some authors, for example, Meyer,<sup>19</sup> may be examples of involvements listed under 2 to 5.

No unique changes are found in the involved appendix or other organs in scarlet fever.

The appendix may be simply enlarged, locally or diffusely reddened, kinked, displaced or intensely hyperemic, boggy, variably necrotic, ulcerated and perforated. The contents may be liquid or semisolid pus with an occasional fecalith. The surface may be covered with simple fibrin

18. Klemm, P.: Ueber die Erkrankung des lymphatischen Gewebes und ihr Verhältnis zur Appendizitis, *Deutsche Ztschr. f. Chir.* 81:42 (March) 1906.

19. Meyer: *Berl. klin. Wehnschr.* 11:488 (March 17) 1913.

to purulent exudate and be enmeshed in adhesions of various degrees of maturity. One, several or all the layers of the wall may become necrotic, leading to scarring and protection of the defect or perforation. The microscopic changes range from simple hyperemia and edema through various degrees of cellular infiltrations (polymorphonuclear, lymphoid and eosinophil) to necrosis of the layers with ulceration, hemorrhage and perforation.

R. Kauffmann (see cases 14 to 18 for reference) claims that the appendix is constantly involved in scarlet fever. According to him the vomiting seen at the onset is due to involvement of the appendix.

Occasionally the lymph nodes between the cecum and ileum are swollen and hyperemic. This reaction may be seen in connection with appendicitis but it often occurs alone.

#### CLINICAL ASPECTS

When one bears in mind that symptoms and signs referable to the right lower abdominal quadrant may arise from several organs, the outstanding rôle of the appendix must be emphasized. To indicate the great susceptibility of this organ to inflammations one may bear in mind Sahli's<sup>20</sup> designation, the "abdominal tonsil."

Two situations in which these inflammatory conditions appear are important:

1. At the onset of scarlet fever the nausea, vomiting and sometimes the abdominal pain may be prominent enough to cause a diagnosis of appendicitis. This diagnosis may be readily possible when one fails to consider the possibility of a contact, the importance of a sore throat or infection of the upper respiratory tract, enlargements of lymph nodes in the neck, axillae and groins and beginnings of a rash in the axillae and groins and elsewhere. There may even be localized tenderness and muscular resistance. There may appear to be enough clinical evidence to justify operation. Soon after this a rash may rapidly develop and point to the true state of affairs. The appendix removed may actually be inflamed, thus bearing out the statement of R. Kauffmann as to the constancy of implication of the appendix. Cases 2, 6 and 8 of the Durand Hospital series indicate how readily one may operate for appendicitis in the face of oncoming scarlet fever.

Paget,<sup>20</sup> Trelat<sup>21</sup> and Martin<sup>22</sup> spoke of scarlet fever following appendectomy. They attributed the cause of the exanthem to the con-

20. Paget, J.: *Scarlatina after Operations*, Brit. M. J. 2:237 (Aug. 27) 1864.

21. Trelat: *De la scarlatine consécutive aux opérations*, Progrès méd. 6:721 (Sept. 14) 1878.

22. Martin, A.: *Scarlatine traumatique dans une appendectomie*, J. de méd. de Paris (series 2) 15:425 (Oct. 18) 1903.

amination of the operative wound with the appropriate organisms. The "surgical scarlet fever," so called by them, may well be that in which the prodromal symptoms mislead one to sole consideration of appendicitis instead of indications of scarlet fever setting in from the first.

2. The abdominal disorder may appear at any time after the onset of the illness and with or without any of the complications commonly associated with scarlet fever. This is seen in cases 1, 3, 4 and 7, in which the abdominal symptoms appeared as transitory events, by case 5, in which they were of considerable importance, and by case 9, in which operation was necessary.

Whenever abdominal symptoms and signs appear with any degree of persistence, appendicitis must be considered with all its implications of perforation and peritonitis.

Some of the clinical pictures that may appear are: The patient is scarcely over the preliminary symptoms and signs, convalescing or suffering from some common complication when he begins to complain of abdominal pain, usually with nausea and often with vomiting. The pain at first is usually diffuse, but it quickly centers in the right lower quadrant. The abdominal wall in that region may become tender and resistant to touch. The temperature, pulse rate or white cell count, or all three together, may be elevated. So far the attack may regress spontaneously and the diagnosis be in doubt. The attack may persist with intensification of all the symptoms and signs. Operation may be considered and performed. There may be hesitation, temporizing or poor observation and judgment of the course of the patient. Then the pain may become diffuse over the entire abdomen, the parietal wall generally tender and much resistant to palpation, the temperature septic, chills and sweats, the respirations faster and more shallow and the pulse rapid and weak. Obstipation, protracted vomiting, prostration and collapse may appear. Usually death occurs from generalized peritonitis secondary to perforation of the appendix, breakdown of the suppurating lymph node or ulceration and perforation of a lymphoid patch of the bowel.

The changes in temperature, pulse rate and white cells may be obscured by the presence of lymph node, middle ear and mastoid, pulmonary, pleuritic, joint, pericardial and other complications. In case 9 of this series the presence of diabetes and serum sickness made the diagnosis especially difficult.

It is of interest to direct attention to the fact that appendicitis may occur in several members of a family in a short time. This is thought by some to be due to a common sharing of some congenital defect. R. Kauffmann suggested that the several members were exposed to scarlet fever and made readily susceptible to appendicitis.

## TREATMENT

When the presence of appendicitis is suspected the condition should be managed like the disease in general. One considers the qualitative, quantitative and chronological content and variations of the illness. The possibility of spontaneous regression under cautious and noninterfering observation is balanced against that of perforation and peritonitis. If the diagnosis is at all obscure, it is probably better on the whole to investigate with laparotomy. Even when the diagnosis of appendicitis appears certain, one may encounter merely ileocecal adenitis, an inflamed and stiffened ileum<sup>23</sup> or inflammation of a lymphoid mass elsewhere and a normal appendix. If such is the case, nothing further should be done. Lewis states that in all these cases operation should not be performed, but he emphasizes the great difficulty of an accurate diagnosis.

## SUMMARY

About 73 cases of appendicitis and a small number of cases of other acute inflammatory conditions of the abdomen in scarlet fever were reviewed. Nine (of which 1 was personally observed by the author) are from the records of the Durand Hospital; the remainder are from the literature available and from communications.

The incidence appears to be small but is likely larger.

The disorders comprise inflammation of the appendix and of various mesenteric lymph nodes and masses of lymphoid tissue elsewhere in the abdomen. The relation of these conditions to involvement of the entire lymphoid system in scarlet fever has been indicated.

The pathogenesis is unknown, but the theory of infection through the blood stream spread and from the throat is plausible.

The anatomic changes do not appear to have any special features.

All these inflammations give nearly an identical picture which is principally that of pathologic involvement of the right lower abdominal quadrant. Two considerations are important: 1. The abdominal manifestations of scarlet fever at the onset may be sufficiently prominent to mislead one in the diagnosis of the oncoming exanthem. 2. When the symptoms and signs appear somewhere during the course of the fever appendicitis must be carefully considered.

The treatment is the same as that for appendicitis in general.

In the generally obscure background of the etiology of appendicitis as it may occur in any person or in several members in a family the presence of scarlet fever must be considered.

23. Rockey, E. W.: Thickening of Terminal Ileum with Mesenteric Adenitis in Children. *Northwest Med.* 32:145 (April) 1933. Lamson, O. F.: Mesenteric Lymphadenitis and Acute Appendicitis, *S. Clin. North America* 11:1061 (Oct.) 1931.

# SUBACUTE LYMPHOGRANULOMA INGUINALE

REPORTS OF TWO CASES

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The purpose of this paper is to emphasize the incidence of lymphogranuloma inguinale on the Pacific Coast. Especially a disease of tropical regions, where it has been abundantly described as climatic bubo, the disease has recently been reported from many European maritime cities and from ports of the Great Lakes.

In the confusion of names the disease should not be confounded with that termed "lymphogranulomatosis," a term often applied to Hodgkin's disease, or with those termed "ulcerative, pudendal disease" and "granuloma inguinale," presumably caused by protozoan infection.

Complete and easily accessible descriptions of the disease are contained in the articles by De Wolf and Van Cleve,<sup>1</sup> Sulzberger and Wise<sup>2</sup> and, especially from the standpoint of pathology, Lillie.<sup>3</sup>

Described briefly, the disease is a venereal infection caused by virus, showing a slight, transitory, mostly unobserved primary genital lesion of ulcerative or nodular type two or three weeks after exposure. This is followed by suppurative adenitis and periadenitis of the inguinal nodes. The livid and tender inguinal mass attains considerable size and softens and drains by a persistent sinus formation. Involvement of the deeper iliac chain occurs; in the later healing fibrotic process strictures of the rectum are apt to follow. These are especially common in women in whom primary infections in the cervix often result in the absence of the inguinal mass, the lymphadenitis affecting only the deep nodes. The course of the disease is from subacute to chronic, locally troublesome,

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From the Department of Surgery and Pathology, St. Luke's Hospital.

1. De Wolf, H. F., and Van Cleve, J. V.: Lymphogranuloma Inguinale, J. A. M. A. **99**:1065 (Sept. 24) 1932.

2. Sulzberger, M. B., and Wise, Fred: Lymphopathia Venereum, J. A. M. A. **99**:1407 (Oct. 22) 1932.

3. Lillie, R. D.: Inguinal Lymphadenitis with Special Reference to the Group Known as Climatic Bubo, Arch. Path. **8**:19 (July) 1929.

and with slight to moderate general symptoms of chills, fever, malaise and pain. Barring rectal stricture it is without serious sequelae.

The Frei test, a local reaction to an intradermal injection of 0.1 cc. of preserved pus in phenol from a known case of the disease, appears to be specific and persistent for years. The pathologic process in the involved glands is that of a tuberculoid reaction with, however, more remains of pus cells in the necrotic areas than are found in tuberculous caseation, with relatively few giant cells and often with hemorrhage or deposit of hemosiderin from an old hemorrhage. Epithelioid cells are variable in abundance, and pronounced fibrosis marks the later stages of the disease. Obliterative endarteritis is absent or less marked than in a syphilitic lesion. Barring secondary infection, bacteria are not found in smears or cultures as they are in chancroidal bubo, in the bubo of bubonic plague and in pyogenic lymphadenitis. The virus appears to be transmissible to mice and to monkeys,<sup>4</sup> at least. Transmissibility to other animals is yet uncertain.

#### REPORT OF CASES

The following reports illustrate the main features of the disease:

CASE 1.—J. B. K., aged 43, white, a sea captain, consulted one of us (A. W.) on July 7, 1932, with regard to a lump in the left inguinal region of three weeks' duration. His familial and personal history were irrelevant, except that during the last three and a half years he had been sailing to and from the Orient and had had a certain amount of time ashore in the East.

His present illness began three days out from Hong Kong with the development of headache, chilliness, pain in the lower part of the back, some coughing and profuse perspiration. He thought that he had a fever also. These symptoms gradually subsided with the exception of the headache and backache, which persisted almost to the time he came for consultation. Four days after the onset of these symptoms, he noticed a lump in the left inguinal region which was slightly sore and which had gradually become more painful and larger since it was first noticed. During the preceding two weeks he had lost about 10 pounds (4.5 Kg.).

The patient was a self-contained person who did not pay much attention to his symptoms. A general physical examination showed no abnormal condition with the exception of that in the left groin. Here was a mass 3 by 2 inches (about 7 by 5 cm.), slightly reddened, with three or four dark pigmented spots  $\frac{1}{2}$  inch (about 1 cm.) in diameter. The dark areas were fluctuant, and the skin appeared to be attached to the underlying mass. Over the remainder of the swelling the skin appeared to be reasonably movable. The mass was definitely superficial to the inguinal fascia, and the finger could be inserted into the external inguinal ring and felt to be definitely beneath this mass. The patient's temperature was 102 F., and he looked much sicker than would be expected from an inflammation of this size. A blood count showed: red blood cells, 4,730,000, and white blood cells, 19,000, with polymorphonuclears 80 per cent. The hemoglobin concentration was

4. Levaditi, C.: Ravaut, P.: Lepine, P., and Schoen, R.: Etude etiologique et pathogenique de la maladie de Nicolas et Favre, *Ann. Inst. Pasteur* 48:27 (Jan.) 1932.

80 per cent. The urine contained albumin, a trace of acetone, occasional hyaline casts, white blood cells and numerous mucous threads.

The patient was admitted to St. Luke's Hospital that afternoon, and a small amount of pus was aspirated from the inguinal region on two occasions. The specimens showed pus cells and fibrin but no bacteria. A culture was negative. Injections into guinea-pigs also gave negative results, and the blood cultures remained negative.

During the first two weeks in the hospital his temperature continued to fluctuate between 102.2 F. and normal, gradually subsiding to normal. Treatment included the application of hot compresses and irradiation with ultraviolet rays from an air-cooled, quartz mercury vapor arc lamp, alpine light but no antimony compounds. One area in the groin broke down completely under treatment. The entire mass of glands in the left groin was then excised under general anesthesia. The glands lay entirely superficial to the external oblique fascia and were adherent in many places to the overlying skin. The skin was removed with the glands in a single block of tissue. The glands extended from just above the inguinal ligament to the saphenous opening. The wound was left wide open, and packed with gauze saturated with potassium permanganate.

The pathologic report on this tissue (W. P. S.) was as follows: Paraffin sections from the inguinal node showed a loss of lymphoid tissue and diffuse fibrosis in some fields and areas of caseation in others. Foreign body giant cells were present in small numbers. Endothelial proliferation of Hodgkin's type and epithelioid cells of the tubercle type were not found. While caseation, giant cells, round cells and fibrosis were all present, in no place were they arranged in typical tubercle formation. This histologic condition was consistent with lymphogranuloma inguinale (tropical bubo), with the possibility of atypical tuberculosis.

In a few days the pack was removed, and the wound was treated with equal parts of castor oil and balsam of Peru.

The patient made an uneventful recovery following the excision of the glands, and was discharged from the hospital seventeen days later with the wound almost entirely healed.

CASE 2.—J. W., aged 42, white, a radio engineer, consulted one of us (B. C. N. O'R.) on Feb. 21, 1932, stating that in the previous April or May he was standing astride a heavy machine cover and attempted to lift it. His left foot slipped, and he felt a sudden severe pain in his left groin. He examined the area, but found no unusual lumps or signs, and in half an hour the pain disappeared. Three or four days later, on examining this same region, he found a painful area which he thought was due to irritation by his clothing. He suspected that he had a rupture and consulted a doctor, who told him that he had not, but said that he had an enlarged inguinal gland, attributable to a small pustule on his buttock. In about ten days the lump in the groin disappeared.

On Feb. 7, 1933, he noticed the lump again, and at this time had chills and slight fever for about a week. He made several attempts through the Industrial Accident Commission to have his disability connected with his original strain, all of which were unsuccessful. On further questioning we found that in 1926 he had been employed on a vessel calling at various ports in the Bay of Bengal, and that he had had swollen glands in the left groin for about two weeks. He stated that he used hot compresses and the swelling "came to a head and pus ran out and then healed." In 1927 the shipping company employing him wished to send him to a hospital in England for a diagnosis, but the patient refused this since the swelling in the groin had disappeared.

Examination showed the general physical condition to be normal, with the exception of the left groin, in which there were enlarged, fluctuating glands. The skin over them was dusky and adherent. There was little redness or other evidence of inflammation. The glands were tender. Exposure to venereal diseases was denied. The blood showed: a hemoglobin concentration of 90 per cent; red blood cells, 4,710,000 per cubic millimeter; color index, 0.96; white blood cells, 10,640 per cubic millimeter, with polymorphonuclears, 67; small lymphocytes, 18; large lymphocytes, 6, and transitionals, 7 per cent. The Wassermann, Kolmer and Kahn reactions were negative. The deep iliac nodes were distinctly enlarged and palpable.

The patient was admitted to St. Luke's Hospital with a diagnosis of lymphogranuloma inguinale, and was tested with Frei's antigen, which had been furnished the hospital by Dr. H. F. de Wolf of Cleveland. The results of the intradermal tests showed, first, an itching and burning, with a 9 cm. area of erythema appearing fifteen minutes after the injection and fading in thirty minutes, and second, at seventy-two hours a 5 cm. wheal with a central papule.

The patient refused to allow surgical intervention at that time, but returned three weeks later for operation. The operative procedure was as follows: The inguinal incision was made around a mass of inguinal glands in the groin. These were easily freed from the external oblique fascia, which was exposed and left bare. Some glands, down at the external inguinal ring, were included in the resected tissue, and two or three were excised from the saphenous opening. The femoral vessels were seen, but were not injured. There were two discolored areas of skin which were attached to the underlying necrotic gland tissue. The upper area was included in the resected mass by extending the incision to surround it, making the incision elliptical. The lower area of the two was below the fold of the groin, and because by inclusion of this area the scar would be drawn crossing the inguinal fold it was not removed, but the glands were scraped away from underneath so that only the skin was left.

The pathologic report (W. P. S.) was as follows: There was a mass of gland and periglandular tissue from the groin, consisting of fatty and fibrous tissue and two broken-down glands, the larger about 2 cm. across, partly fibrous and with multiple foci of soft, creamy, caseous-looking material, each about 1 mm. across. Cultures of this material were sterile after ten days' incubation. Smears were negative for acid-fast bacilli. Sections showed the lymphoid tissue markedly reduced by replacement by a formation resembling a tuberculoïd granuloma. In many fields there was diffuse, dense, almost hyaline, fibrosis. In others the granulomatous foci took the form of caseous centers surrounded by a few epithelioid cells; outside of this was a sharp zone of fibrosis that quite rapidly became dense in the outer layers. Round cells were represented only by the remains of the lymph node cells, and giant cells of the foreign body type were found only on careful and prolonged search. The adjacent vessels showed thickening and arteritis, but without perivascular round cells.

The various treatments advocated for this disease include tuberculin injections, injection of glycerin into the glands and sinuses, roentgen ray and ultraviolet ray therapy, intravenous injections of 1 per cent solutions of antimony and potassium tartrate and surgical resection. In the cases of rectal stricture, surgically inaccessible, the treatment with antimony certainly should be used. The two cases reported here responded rapidly and perfectly to surgical excision. That such excision is the



method of choice is borne out by the experience of one of us (A. W.). While surgeon at the old Marine Hospital in San Francisco years ago, he saw many sailors with this condition, presenting in the groin dirty, ulcerating, sloughing wounds that had been present for months, and had been treated elsewhere by incision. The wounds were often necrotic and so foul that the man had the sinus packed with oakum to kill the stench. Nevertheless, even these lesions, months old, healed with rapidity following radical excision.

## II. USE OF BACTERIOPHAGES IN TREATMENT OF COLON BACILLUS INFECTIONS OF THE URINARY TRACT

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In offering a brief summary of our experience in the application of bacteriophage therapy to urinary infections with colon bacilli, we are well aware of earlier observations in this field. A review of the earlier work seems superfluous, but we wish to acknowledge our indebtedness to the pioneer studies, and their aid as a guide in our own attempts. Those who have worked in this field have, as a rule, observed some favorable effect, apparently due to the bacteriophage in some instances, and an occasional strikingly favorable result evidently related to the use of this agent. However, there have been many disappointments and unexplained failures, so that some of the workers with extensive experience have lost their early enthusiasm for the use of bacteriophages in this field.

We are inclined to think that some of the failures may have been due to lack of understanding of the limitations of bacteriophage action and to lack of sufficiently intimate and sympathetic cooperation between the clinician and the bacteriologist. From experience in our own series of cases we are convinced that the technic of application of the remedial agent may sometimes determine the issue between success and failure. This point is particularly well illustrated by the work of Dr. George C. Leckie<sup>1</sup> at the Newark City Hospital. This urologist, employing bacteriophages supplied by our laboratory, treated 14 patients with colon bacillus infections of the urinary tract, with 7 recoveries with bacteria-free urine, 6 instances of marked symptomatic improvement with persisting bacilluria and 1 failure.

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These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

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1. The patients of Dr. Leckie are included in our summarized figures. We understand that he will present his detailed observations in a paper of his own.

We have more or less satisfactory records for 388 patients from whom specimens of urine were sent to us for bacteriophage service. In 118 of these specimens the laboratory study revealed no evidence of infection. In 270 bacterial infection was recognized. In these 270 specimens our records indicate the presence of 318 infectious organisms, some of the samples containing 2 or even 3 or 4 different organisms. Table 1 indicates the proportion in which the various types of microbes were found and also gives an analysis of their relative susceptibility. The predominance of *Escherichia acidilactici* is noteworthy. The members of the *Escherichia* group maintained almost the same frequency of resistant strains, but the *Aerobacter* group was almost entirely resistant to the bacteriophages in our collection.

TABLE 1.—*Susceptibility to Phages of Organisms in Urinary Infections*

Organism	Total Strains	Resistant		Partial Lysis		Susceptible	
		Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
<i>Escherichia acidilactici</i> .....	115	13	12	24	21	78	67
<i>Escherichia communior</i> .....	34	6	18	6	18	22	64
<i>Escherichia coli</i> .....	15	2	13	6	40	7	47
<i>Aerobacter</i> group.....	44	43	98	1	2	0	0
Miscellaneous bacilli*.....	55	32	58	9	17	14	25
<i>Staphylococcus aureus</i> .....	11	2	18	0	0	9	82
<i>Staphylococcus albus</i> .....	16	11	68	1	7	4	25
<i>Streptococcus haemolyticus</i> .....	9	9	100	0	0	0	0
<i>Streptococcus</i> (Indifferent).....	7	7	100	0	0	0	0
<i>Streptococcus viridans</i> .....	3	3	100	0	0	0	0
<i>Streptococcus</i> with partial hemolysis.....	9	9	100	0	0	0	0
Totals.....	318	137		47		134	

\* This group consists of atypical *Escherichia*, 35; *Alcaligenes faecalis*, 3; proteus group, 10; *Shigella paradysenteriae* (Flexner), 1, and *Pseudomonas aeruginosa*, 6.

Of the 270 patients with urologic conditions with positive cultures there were 72 in whose specimens of urine organisms of the colon bacillus group were not found and 198 in whose specimens colon bacilli were present. For various reasons bacteriophage therapy was not used for 101 of these patients. The chief reason was our failure to find an effective bacteriophage. However, in 18 instances in which an effective bacteriophage was successfully prepared in the laboratory it was not used in treatment. To 97 patients treatment with bacteriophage was given. For 24 of these we lack adequate information in regard to the result; for 23 there was a report of failure; 27 showed symptomatic improvement without final bacteriologic proof of eradication of the infection, usually because no specimen of urine was submitted, and for 23 there was clinical success coupled with bacteriologic proof of bacteria-free urine. These data are shown in table 2.

A few patients will be considered in some detail in order to illustrate the methods employed and the experiences in success and failure.

## REPORT OF CASES

CASE 1.—C. C., a white woman, aged 43, was admitted to the hospital on Sept. 11, 1929, complaining of pain in the lower part of the abdomen, menorrhagia and urinary frequency. On September 12, the appendix, uterus, tubes and ovaries, except a portion of the left ovary, were removed by Dr. John F. Erdmann. There were multiple fibroids in the uterus and evidence of chronic inflammatory disease of the other organs removed. During the third night after the operation urinary frequency became evident, and the patient complained of irritation in the bladder. The urine specimen passed at 6 a. m. on September 17 contained an excessive number of leukocytes, and on that day and the next methenamine was given. The irritation of the bladder continued. On September 20 the sutures were removed from the abdominal wound, and the patient sat up in a chair for half an hour. Her temperature rose, and she became nauseated, and the urine passed on September 23 contained many pus cells. A specimen of urine obtained by catheterization on the morning of September 24 yielded over 500,000 colonies of colon bacilli per cubic centimeter. When the result of the culture became known, the administration

TABLE 2.—*Patients with Urologic Conditions Classified According to Bacteriologic Diagnosis and Relation to Bacteriophage Therapy*

Total patients .....	353
Patients with negative cultures.....	115
Patients with other than colon bacillus infections.....	72
Patients with colon bacillus infections.....	168
Bacteriophage not used in treatment.....	101
No effective bacteriophage found.....	57
Effective bacteriophage prepared.....	15
Partially effective bacteriophage prepared.....	23
Request withdrawn.....	3
Bacteriophage used in treatment.....	97
Result not adequately reported.....	24
Failure of bacteriophage therapy.....	23
Symptomatic improvement .....	27
Success with bacteriologic proof.....	23

of methenamine was again started and continued until September 28. Disodium monohydrogen phosphate was also given on September 26, 27 and 28. On September 28 the patient had her worst day, with persistent vomiting, a frank chill and a rise of temperature to 105 F. A blood culture taken on this day was negative. The disodium monohydrogen phosphate and methenamine were discontinued, and potassium citrate in 15 grain doses was given in order to get the urine nearly neutral in reaction, in preparation for bacteriophage therapy. The fluid intake was kept at a high level.

Meanwhile the colon bacillus from the urine of September 24 had been found susceptible to bacteriophage, and a bacteriophage specific for this organism had been prepared in broth. A subcutaneous injection of 1 cc. of this broth filtrate was given at 8 p. m. on September 30. At 1:40 p. m. on October 1, a specimen of urine was obtained by catheterization, and 10 cc. of bacteriophage filtrate diluted with 90 cc. of saline solution was introduced into the urinary bladder. The catheterized urine obtained at this time was studied in the bacteriologic laboratory. It was alkaline ( $pH$  7.3), and its cultures yielded more than 500,000 colonies of colon bacilli per cubic centimeter. Serial filtrations of cultures failed to reveal the presence of bacteriophage in the urine. At 6:30 p. m. on this day a second subcutaneous injection of bacteriophage broth was given, this time a dose of 2 cc. On October 2 chemical analysis of the blood showed the urea nitrogen to be 6.9

mg. per hundred cubic centimeters, a low figure. At 2 p. m. on this day urine was again obtained by catheterization, and 10 cc. of bacteriophage diluted with saline solution was again introduced into the bladder. This urine specimen was neutral in reaction ( $p_H$  7), and the plate cultures showed a marked diminution in the number of colonies, there being approximately 125,000 per cubic centimeter. Furthermore the filtrate of this urine exhibited a strong bacteriophage action on cultures of the infecting bacterial strain. Administration of bacteriophage was discontinued. After October 2 the fresh urine specimens, as passed, were frequently tested with litmus paper by the nurse. On October 3 and 4 these tests showed an acid reaction. On October 5, the reaction became neutral and then alkaline, returning to acid on the morning of October 6 and changing to neutral in the afternoon and to acid again on the morning of October 7. On October 8 the morning urine, tested by comparator, showed a  $p_H$  of 6.8. The dosage of potassium citrate was increased to 60 grains (3.6 Gm.) for this day and 75 grains (4.5 Gm.) for October 9. The morning urine of October 10 was distinctly alkaline ( $p_H$  7.4). Bacterio-

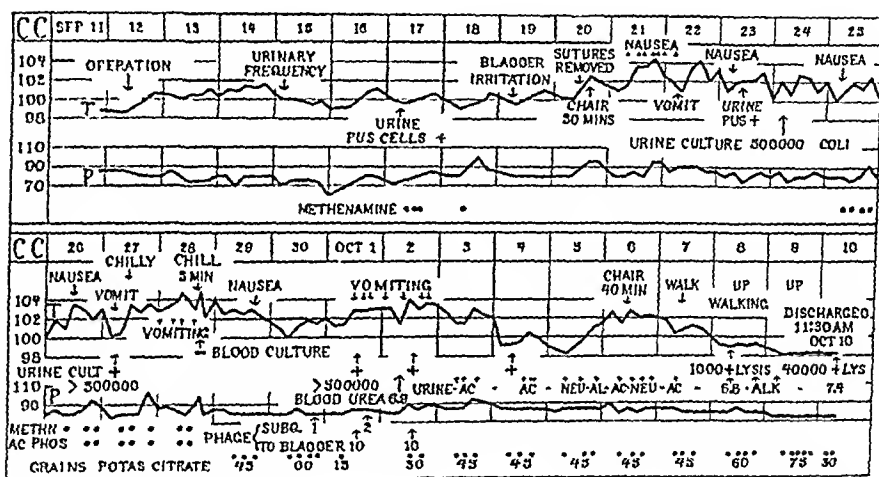


Chart 1 (case 1).—Abridged clinical chart for C. C., showing the course of the temperature ( $T$ ) and pulse rate ( $P$ ) together with outstanding features of the clinical record.

logic study of the morning urine of October 4 revealed many swollen and distorted bacilli in the microscopic preparation. The cultures revealed a further diminution in viable bacteria, there being less than 100,000 colonies per cubic centimeter of urine. The urine filtrate contained a strongly active bacteriophage. The morning urine of October 8 yielded only about 1,000 colonies per cubic centimeter of urine, and these colonies showed the peculiar effects of bacteriophage as they grew on the plates. The broth cultures failed to show any colon bacilli, presenting only contaminating cocci and diphtheroid bacilli. The filtrate revealed the presence of a strongly active bacteriophage. The last urine specimen, obtained on October 10, was almost clear. Its reaction was alkaline ( $p_H$  7.4). The sediment contained pus cells and irregularly stained swollen and distorted bacilli. Plate cultures yielded 40,000 colonies per cubic centimeter of urine. The filtrate of the urine still contained active bacteriophage, but in diminished concentration as compared with the urine of October 8. The lytic agent had, however, persisted in the urinary tract for eight days.

The patient improved clinically from the time the methenamine and disodium monohydrogen phosphate were discontinued on September 28. She was rather miserable on October 1 and 2 and resented somewhat the administration of the bacteriophage. After October 7 she was comfortable, and when discharged on October 10 she was free from symptoms. She has remained well. Our requests for further specimens of urine have not been granted. This patient's condition was classified as acute postoperative pyelitis clinically improved but without bacteriologic proof of success.

CASE 2.—A. R. H., a white woman, aged 31, was admitted to the hospital on Feb. 25, 1930. On this day the appendix was removed, and a constricting band which obstructed the small intestine was released. Following the operation the patient was catheterized at 6 p. m. on the same day and also twice on the following

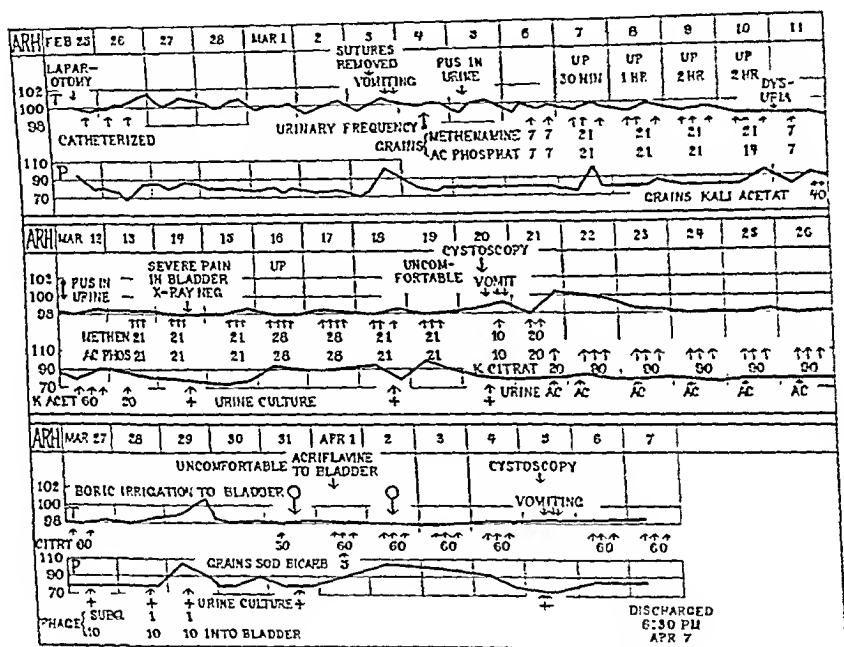


Chart 2.—Abridged clinical chart for A. R. H.

day. The postoperative progress was satisfactory until March 3, when the sutures were removed. Following this there were severe abdominal pain and vomiting at 9:15 and again at 11:15 p. m. On the next day there was a constant desire to void urine, and a foul odor of the urine was noted by the nurse. Clumps of leukocytes were recognized by microscopic examination of the urine on March 5. Methenamine and disodium monohydrogen phosphate were given, beginning on March 6, and the patient was allowed to be out of bed each day from March 7 to 10. Marked dysuria was noted during the night of March 10, and on March 11 the methenamine and phosphate were discontinued and potassium acetate was given. On March 12, clumps of pus cells were found in the urine, as before. Methenamine and acid phosphate were started again on March 13. On March 14 the discomfort in the bladder was severe, and after consultation urine was sent to the laboratory for culture and microscopic examination for tubercle bacilli. Roentgenologic examination of the kidneys on this day gave negative results. The

urine was negative for tubercle bacilli. It contained pus cells and gram-negative bacilli, which on culture proved to be colon bacilli of the lactic acid variety.

The methenamine and disodium monohydrogen phosphate were continued until March 21. Meanwhile a culture of the bladder urine on March 18 confirmed the previous findings. The colonies of colon bacilli on the most dilute plate culture inoculated with 0.05 cc. of urine were too numerous to be counted. There was increasing discomfort on March 19. On March 20 a cystoscopy was done with the patient under nitrogen monoxide-oxygen anesthesia. Opaque catheters were passed into both ureters, and roentgenograms made. These gave essentially negative results. At this time specimens of urine were collected from the bladder and from each ureter. Bacteriologic study of these specimens showed approximately 10,000,000 viable colon bacilli per cubic centimeter in the bladder urine, but both the ureteral specimens were found negative on microscopic and cultural examination.

Following the cystoscopy, the patient vomited three times, and her temperature rose to 100.4 F. on March 21. The methenamine and disodium monohydrogen phosphate were discontinued on this day and administration of potassium citrate was begun. The dose of the citrate was increased to 90 grains (5.4 Gm.) daily, but the urine remained persistently acid in reaction. Meanwhile the culture of colon bacilli had been tested against ten different races of bacteriophage in the laboratory, and the activity of two of these had been enhanced by six serial filtrations. Preparations in broth were made available for therapeutic use. On March 27, at 11 a. m., bladder urine was obtained by catheter, and 10 cc. of the bacteriophage broth diluted with 90 cc. of sterile saline solution was left in the bladder. Apparently through some misunderstanding, the citrate was discontinued at this time. Cultures of this bladder urine of March 27 yielded 100,000 colonies per cubic centimeter, and the organism was tested and found susceptible to the bacteriophage used in therapy. On March 28, at 4 p. m., the bladder was again catheterized and 10 cc. of the bacteriophage broth in 90 cc. of saline solution was left in the bladder. A subcutaneous injection of 1 cc. of the bacteriophage broth was given at this time. This procedure was repeated at 10 a. m. on March 29. A moderate rise in temperature was apparently caused by the subcutaneous injections. Bacteriologic study of the urine specimens of March 28 revealed no pus cells and no recognizable bacteria on microscopic study, but the cultures yielded 20,000 colonies per cubic centimeter of urine. These bacteria were found by test tube experiment to be susceptible to the phage used in therapy. The catheterized specimen of March 29 revealed cellular debris and bacilli on microscopic study, and the cultures yielded more than 10,000,000 colonies per cubic centimeter of urine. This organism was now found to be resistant to the bacteriophage in the test tube. However, when grown on agar plates the strain revealed plaque formation, and by serial filtration of broth subcultures a bacteriophage highly potent against stock laboratory cultures was again recovered. On March 31, at 3:30 p. m., a catheterized specimen of urine was taken. Cultures of this yielded 70,000 colonies per cubic centimeter of urine. The organism was found to be resistant to the bacteriophage in the test tube.

Immediately after the collection of the last mentioned specimen the bladder was irrigated with boric acid solution. On April 1 at 9 a. m. a solution of acriflavine base was left in the bladder, and on April 2 another irrigation with boric acid was given at noon. The administration of potassium citrate, which had been interrupted on March 27, possibly because of some erroneous idea on the part of the physicians that the citrate might be incompatible with bacteriophage, was continued after March 30, and on April 1 it was supplemented with soda.

On April 5 at 8 a. m. the bladder was catheterized, and at 8:30 a. m. on the same day cystoscopy was done with the patient under nitrogen monoxide-oxygen anesthesia, another specimen of bladder urine being taken at this time. The cystoscopic examination gave essentially negative results. The first specimen of bladder urine (8 a. m.) contained many pus cells and moderately numerous bacilli in the sediment. Cultures yielded 1,500,000 colonies per cubic centimeter. These bacteria were found to be resistant to the special bacteriophage prepared for this patient and to twenty-one other races of colon bacteriophages in the laboratory collection. The second bladder specimen, taken at the time of cystoscopy (8:39 a. m.), was clear and contained no recognizable leukocytes. Only 4 bacilli were found in the microscopic smear of the sediment. Cultures yielded only 15,000 colonies per cubic centimeter.

The record of this patient illustrates a difficulty which may arise when a bacteriophage is used to treat urinary infection without adequate care in regulating the reaction of the urine. It is possible, however, for resistant variants to develop in the patient even when the reaction of the urine is intelligently controlled. This

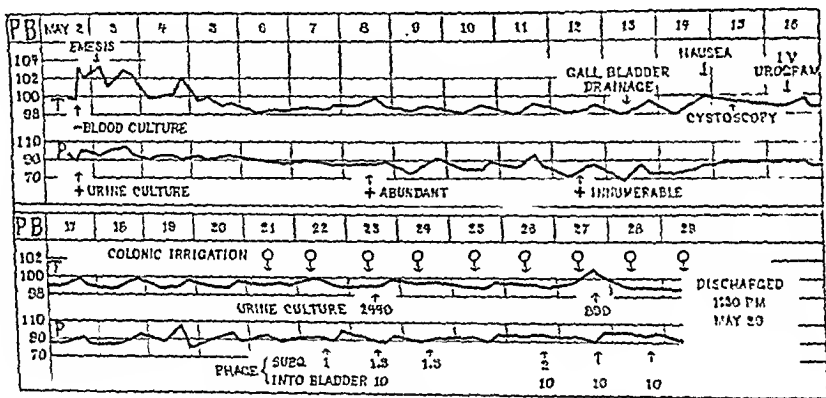


Chart 3.—Abridged clinical chart for P. B.

patient's condition was classified as postoperative cystitis with failure of bacteriophage therapy.

CASE 3.—P. B., a white woman, aged 43, was admitted to the hospital on May 2, 1931, complaining of chills and fever lasting for about three days, associated with pain in the lower part of the abdomen and recurring at intervals of about three weeks during the last four months, sometimes associated with the menstrual period. A blood culture taken on May 2 was negative, but a culture of the urine yielded a growth of colon bacilli of the lactic acid variety, and there were moderately numerous leukocytes in the urine. The patient experienced what was apparently a typical attack of her disorder and improved by May 5. Numerous diagnostic procedures, including agglutination tests for tularemia, typhus and undulant fever, search for the organisms of malaria, basal metabolism tests and drainage of the gallbladder gave negative results. Roentgenograms of the kidneys, however, revealed a small, atrophic right kidney and a normal left kidney. Culture of the urine repeated on May 8 and again on May 12 gave abundant growth of colon bacilli. A series of colonic irrigations was begun on May 21, and potassium citrate, 15 grains (0.9 Gm.), was given on this day, preliminary to the use of bacteriophage which had been prepared. On May 22 three doses of potassium



citrate, total amount 60 grains (3.6 Gm.), were given, and the patient received a subcutaneous injection of 1 cc. of colon bacteriophage broth at noon. On the next day she was given a subcutaneous dose of 1.5 cc. and into the bladder 10 cc. of bacteriophage broth diluted with sterile saline solution. Bladder urine taken just preceding this instillation yielded 2,440 colonies of colon bacilli per cubic centimeter. The subcutaneous injection of bacteriophage was repeated on May 24 and on May 26, with instillation into the bladder on May 26, 27 and 28. Culture of the urine on May 27 yielded 890 colonies per cubic centimeter. The patient was discharged on May 29. She returned to the outpatient department and received intravesical instillations of bacteriophage on June 2, 4 and 16 and an intravesical instillation of 1:8,000 silver nitrate solution on June 23. From July 3 to 6 she was again in the hospital and, under nitrogen monoxide-oxygen anesthesia, received local injections of alcohol for relief of pruritus vulvae. Again in the outpatient department she received intravesical instillation of bacteriophage on July 14, 21 and 23. The specimen of bladder urine taken before treatment on May 27 yielded 890 bacterial colonies per cubic centimeter; that of June 2 yielded 3,780; that of June 4 yielded 620; that of June 15 yielded 7,270, and those of July 21 and July 23 gave no growth.

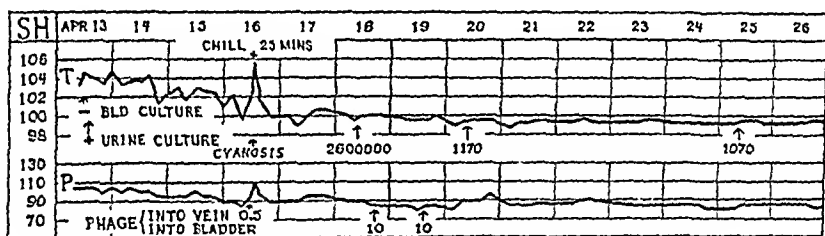


Chart 4.—Abridged clinical chart for S. H.

This patient's condition was classified as chronic recurrent pyelitis successfully treated with bacteriophage.

CASE 4.—S. H., a graduate nurse, after exhausting service at private duty became ill on April 6, 1932, with painful and frequent micturition. On April 8 she had a severe chill and rise of temperature to 103 F. Constipation had been marked since March 30. She was admitted to the hospital on April 13. On this day a blood culture was found to be negative. Culture of the urine revealed innumerable colon bacilli of the lactic acid variety. Methenamine was given by mouth and also intravenously on April 13 and 14, after which it was discontinued. Potassium citrate was given, 40 grains (2.4 Gm.), on April 15, 20 grains (1.2 Gm.) on April 16, 40 grains (2.4 Gm.) on April 17, 35 grains (2.1 Gm.) on April 18, 60 grains (3.6 Gm.) on April 19 and 40 grains (2.4 Gm.) on April 20. The fluid intake was kept at a high level. Each specimen of urine was tested when fresh with blue and red litmus paper, and the morning and evening specimens were tested with phenol red and bromcresol purple with appropriate comparators to determine more precisely the hydrogen ion concentration. The dosage of the citrate was changed so as to keep the urine nearly neutral in reaction after April 15.

At 11:48 a. m. on April 16, an intravenous injection of 5 cc. of a 1:10 dilution of colon bacteriophage in asparagine was given intravenously in one hundred and thirty-five seconds. At 12:35 p. m., or forty-seven minutes after this injection

was started, the patient had a severe chill, complained of ringing in the ears and became very cyanotic. The rigor lasted for twenty-five minutes. At 1:30 p. m. the temperature was 105.8 F., the pulse rate, 110, and the respiratory rate, 20. At 2 p. m. there was profuse diaphoresis, and at 4 p. m. the temperature was 101.6 F. A catheterized specimen of urine obtained at 10 a. m. on April 18 was nearly neutral in reaction ( $p_H$  6.9), and plate cultures showed 2,600,000 colonies of colon bacilli per cubic centimeter. Moderately numerous swollen bacteria were seen in the microscopic examination, but recovery of the bacteriophage from this urine by serial filtration of broth cultures was not attempted. At 6 p. m. on this day the bladder was irrigated with 1 liter of boric acid solution, and then 10 cc. of bacteriophage broth diluted with saline solution was introduced into the bladder and retained until 9 p. m. The urine voided at 9 p. m. was clear. On April 19 at 3 p. m. the bladder was again irrigated with a liter of boric acid solution, and bacteriophage broth was left in the bladder as before. On April 20 at 9:30 a. m. a catheterized specimen of urine was obtained and examined. The cultures brought to development 1,170 colonies per cubic centimeter of urine. After the taking of the specimen, the bladder was irrigated with a liter of boric acid solution which returned clear. The patient was comfortable and was up in a chair for a short time on this day. The bladder was irrigated with a liter of saline solution on April 21 and with a similar quantity of boric acid solution daily from April 22 to 28, inclusive. Preceding the irrigation on April 25, a urine specimen was taken for culture, and it yielded 1,070 colonies per cubic centimeter. Some of these colonies presented marginal defects, indicating the presence of active bacteriophage. Shortly after her discharge from the hospital on April 28, the patient returned to duty as a nurse.

On May 16 and again on December 5 bacteriologic examination of her bladder urine showed it to be free from bacteria. This patient's condition was classified as acute pyelitis with successful outcome of treatment confirmed by bacteriologic examination.

#### COMMENT

From the numerous cases of urinary infection we have selected these 4 as examples of success and of failure in acute and in chronic forms of this disorder. Pyelitis does not ordinarily present a serious threat to the life of the patient, and frequently it may permit a moderate amount of efficient activity. On this account, the patient and perhaps also his physician may not care to make too great a sacrifice in order to eradicate the infection. It is also evident that some urinary infections with colon bacilli are due to strains for which active bacteriophages are not now available. Furthermore, it sometimes happens that the infecting bacterial strain, at first susceptible to lysis by bacteriophage, later acquires a resistance to this agent. We do not, therefore, regard bacteriophages as panaceas for urinary infections with the colon bacillus. The hasty application of these agents without consideration of their limitations may be expected to lead to frequent disappointment. Particularly will this be the case when they are applied without adequate fluid intake and without attention to the chemical reaction of the urine, with simultaneous use of internal urinary antiseptics such as methenamine or in combination with repeated superfluous cystoscopic and ure-

teral instrumentation. On the other hand, when employed with intelligence and care and adequately controlled by continued laboratory studies throughout the course of treatment, the bacteriophages may often be of help and occasionally appear to bring about a dramatic favorable result.

#### SUMMARY

1. The results of bacteriophage treatment of urinary infections with colon bacilli have been highly irregular.

2. Some failures appear to be explained by the presence of resistant bacterial strains or bacterial strains which acquire resistance during the course of treatment.

3. Many failures in our series have obviously been due to a lack of sustained interest and of adequate sympathetic cooperation on the part of the patient, the clinician and the bacteriologist.

4. The technic of administration of bacteriophage and the adequate control of accessory therapeutic measures play a large part in determining success or failure.

5. Properly applied in properly selected cases of urinary infection, the bacteriophages add something of real value to the therapeutic armament in the urologic field.

# ABSORPTION OF DEXTROSE AND WATER BY THE SMALL INTESTINE AND THE COLON

## AN EXPERIMENTAL STUDY

REGINALD A. CUTTING, M.D., C.M., PH.D.

NEW ORLEANS

In view of the great importance in the practice of medicine of an adequate understanding of the normal processes of absorption from the gastro-intestinal tract, one is rather surprised to find that many hiatuses exist in the knowledge of this function—hiatuses that involve rather basic considerations. This is particularly true with reference to the absorptive activities of the large bowel, concerning which comparatively few facts are known for certain and much of the experimental investigation of which is inconclusive.

No one can question the ability of the large bowel to absorb certain substances, e. g., certain anesthetic substances, because of the characteristic train of symptoms which follow their administration and which could occur in no way other than as a result of absorption. Thus, one who has even once seen rectal anesthesia from ether or avertin has seen spectacular and incontrovertible evidence of specific colonic absorption.

Unfortunately, however, from the point of view of a knowledge of the colonic absorptive function, many of the other substances which the physician would like on occasion to introduce into the rectum for absorption produce no such spectacular or specific effects as are produced by drugs of the anesthetic type, and in dealing with the possibility, likelihood or extent of absorption of such substances resort must be taken to indirect methods, precise scientific calculations and an ample series of control observations.

That the rectum and colon are capable of absorbing significant quantities of water and certain simple salts, such as sodium chloride, sodium bromide, ammonium chloride and sodium iodide, seems to be generally, though not universally, admitted.

The ability of the rectum and colon to absorb the common, simple sugar, dextrose, however, is much doubted by many investigators, despite numerous excellent experimental efforts to settle the matter and a universal agreement that occasionally rectal administration of dextrose would be highly desirable clinically if it could be shown to be feasible.

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## CRITICAL REVIEW OF PREVIOUS FINDINGS AND METHODS OF INVESTIGATION AS RECORDED IN THE LITERATURE

Exhaustive reviews of the literature on this subject have appeared in print, notably the recent excellent one of Ebeling,<sup>1</sup> and no good purpose would therefore seem to be served by a mere repetition of previous experimental findings according to author and year of publication. Inasmuch, however, as the experimental findings have been by no means conclusive, first, because the actual results obtained by similar methods of study but by different investigators have yielded almost diametrically opposite conclusions and, second, because in many instances the methods of experimentation have been open to more or less obvious and serious fundamental criticism, it seems desirable, even at the risk of repetition, to marshal again the results of previous investigators, but arranged in such a manner as to expose possible sources of error, and arrive, if possible, at a tentative conclusion which will, so far as possible, reconcile apparent discrepancies.

In general, two methods of attack have been used in investigating the problem: (a) the indirect and (b) the direct.

In the indirect attack, dextrose solutions of known concentration have been introduced into the large bowel by way of the anus in human beings and experimental animals, and the absorption of the dextrose has been measured by repeated estimations of the blood sugar or by repeated measurements of the respiratory quotient.

In the direct attack, solutions of dextrose of known concentration have been introduced into the rectum in human beings or into segments of intestine isolated at laparotomy under general anesthesia in animals, and later have been recovered and analyzed, the difference in amount between the injected and the recovered dextrose being taken as the measure of the absorption—the “wash-out method.”

*Results Obtained by Indirect Methods.*—Method Based on Estimations of Blood Sugar: The greatest volume of experimental evidence has been collected on two assumptions: (1) that the blood sugar content necessarily increases whenever absorption of dextrose occurs from any part of the gastro-intestinal tract, and (2) that the blood sugar value is a function of dextrose absorption—that when absorption of dextrose occurs at a given rate the blood sugar value shows a definitely corresponding increase.

1. Some investigators have drawn conclusions from estimations of the peripheral venous blood sugar.

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1. Ebeling, W. W.: Absorption of Dextrose from the Colon, Arch. Surg. 26:134 (Jan.) 1933.

Using human subjects, Tallermann<sup>2</sup> injected 180 cc. of 33 per cent dextrose solution slowly into the rectum, and found that slight slow increases in the peripheral blood sugar occurred.

Varela and Rubino<sup>3</sup> gave retention enemas of 40 per cent dextrose solution to human beings, and concluded from peripheral blood sugar determinations and from urinalyses that minute amounts of dextrose were soon absorbed, but that the solution was not tolerated long and was soon expelled.

Franke and Wagner<sup>4</sup> introduced 25 Gm. of dextrose in the form of 50 per cent solutions into the rectum in dogs and determined the peripheral blood sugar level at the end of fifteen, thirty, forty-five and sixty minute intervals. These authors found little, if any, effect on the blood sugar level.

Levi<sup>5</sup> injected 500 cc. of solutions of dextrose varying in strength from 10 to 16 per cent into the colons of (1) normal men during fasting, (2) diabetic patients and (3) patients recently subjected to major surgical operations, and found that peripheral blood sugar estimations indicated individual differences in absorptive power, but that in general only small quantities of dextrose seemed to be absorbed.

Pressman<sup>6</sup> introduced 33 per cent solution of dextrose into the rectum in human beings, and found that this caused a decrease in the peripheral blood sugar.

De Takáts<sup>7</sup> found that the introduction of large quantities of 5 per cent solution of dextrose under the skin or into the mouth caused increases in the peripheral blood sugar, whereas the introduction of such a solution directly into the blood stream caused a decrease in the peripheral blood sugar during a period of two hours.

Scott and Zweighaft<sup>8</sup> examined the peripheral blood sugar level in medical students following rectal administration of hypertonic solutions of dextrose. They found no increase in the blood sugar after the

2. Tallermann, K. H.: On the Rectal Absorption of Glucose, *Quart. J. Med.* **13**:356 (July) 1920.

3. Varela and Rubino: *Rektale Dextrose Zufuhr und Blutzucker*, *Med. Klin.* **18**:831, 1922.

4. Franke, W., and Wagner, R. J.: Studies on the Fermentable Blood Sugar After Parenteral and Rectal Administration of Glucose, *J. Metab. Research* **6**:375, 1924.

5. Levi, D.: A Note on the Glucose Enema and Its Value in Postoperative Treatment, *Brit. J. Surg.* **15**:282, 1927.

6. Pressman, J. J.: Absorption of Glucose per Rectum, *Am. J. M. Sc.* **179**:520, 1930.

7. de Takáts, G.: Push Fluids: Surgeon's Postoperative Order, *Am. J. Surg.* **11**:39, 1931.

8. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administrations of Dextrose, *Arch. Int. Med.* **49**:221 (Feb.) 1932.

administration of 180 cc. of a 15 per cent or a 30 per cent solution, a decrease of about 10 mg. per hundred cubic centimeters of blood after the administration of 200 cc. of a 10 per cent solution and a decrease of 7.5 mg. per hundred cubic centimeters of blood after the administration of 400 cc. of a 10 per cent solution.

Such experimental results are inconclusive for at least three reasons:

(a) Authorities are not agreed that the peripheral blood sugar varies in parallelism with the intestinal absorption of dextrose.

Cori<sup>9</sup> concluded after investigating the alimentary absorption of dextrose that the peripheral blood sugar level cannot be used as a measure of intestinal absorption.

Ebeling<sup>1</sup> concluded that estimations of the blood sugar are not accurate criteria of the intestinal absorption of dextrose, at least when the rate of absorption is slow, i. e., that there is no correlation between the blood sugar level and the rapidity or the extent of absorption.

Magee and Reid<sup>10</sup> concluded, on the other hand, that the peripheral blood sugar level can be used as a measure of intestinal absorption. They found at a time when no intestinal absorption was occurring that the portal and systemic blood sugar values were practically identical, whereas within about three minutes after a solution of dextrose had been ingested the portal blood sugar showed an increase of approximately 20 mg. per hundred cubic centimeters, and that this general disproportion was maintained throughout the period of absorption; however, inasmuch as both levels rose, the systemic blood sugar level was as good an index of absorption as the portal level.

(b) Almost without exception, intensely hypertonic solutions have been used, and, reasoning from the established action of other hypertonic solutions in the intestinal tract, one would expect, at least as a primary action, abstraction of water from the intestinal capillaries or tissue spaces to occur rather than absorption of the solute. That this is exactly what does happen when hypertonic solutions are used is suggested by the accurate clinical observation that such solutions are irritating (i. e., their bulk soon becomes intolerable), and that they are expelled.

(c) Finally, judged purely on their own merits, the results are inconclusive inasmuch as some increase in peripheral blood sugar has been found by a number of investigators, no increase by others, and even a depression of the peripheral blood sugar by still others.

2. Recently several investigators, using experimental animals, have attempted to draw conclusions from estimations of the blood sugar in

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9. Cori, C.: Mammalian Carbohydrate Metabolism, *Physiol. Rev.* **11**:143, 1931.

10. Magee, H. E., and Reid, E.: Absorption of Glucose from the Alimentary Canal, *J. Physiol.* **73**:163, 1931.

samples taken from the radicals of the portal system draining isolated loops of intestine in which solutions of dextrose had been placed.

Inasmuch as these experiments have been combined with observations by the "wash-out" or direct method, they can best be detailed under the heading of the latter a little later. These experiments have seemed to show that little if any absorption of dextrose occurs compared with that occurring in the ileum.

For the present it will suffice to mention some of the possible shortcomings of such a method:

(a) All such experiments involve anesthesia, laparotomy, trauma to the intestine and its blood vessels, some hemorrhage, and usually difficulty in obtaining adequate quantities of blood for proper analysis. Anesthesia and operative manipulations, at least, cause variations in the blood sugar level, as I shall demonstrate later by my own experiments.

(b) The experimental conditions involve the absorption of water and dextrose; since the dextrose is supplied in solution, obviously the absorption of a considerable amount of water vitiates quantitative estimation of the absorption of dextrose, for the concentration of dextrose which is taken as the measure of absorption is affected by the dilution, a simple fallacy but one which seems to have been completely overlooked.

(c) Such a method would fail entirely to show the absorption of dextrose if the absorption were sufficiently slow, for the experimental error in blood sugar analysis would mask it completely, and an amount of absorption which might be slight in an hour or two and after an extensive intra-abdominal operation might be considerable in a period of several hours, especially in a patient not subjected to laparotomy.

Method Based on Effects on the Respiratory Quotient: Other

investigators have used the respiratory quotient to measure absorption. Hari and Halasz<sup>11</sup> tied a ligature tightly about the ileocecal valve in dogs and after introducing solutions of dextrose through the rectum found only slight increase in the respiratory quotient.

In two experiments on human beings, Carpenter<sup>12</sup> administered retention enemas of 30 Gm. of dextrose in 500 cc. of physiological solution of sodium chloride. Within two or three hours, the respiratory quotient changed from 0.02 to 0.05, and a considerable portion of the dextrose originally introduced could not be recovered by washing the rectum (17.5 Gm. in one case and 26.3 Gm. in the other).

That the respiratory quotient is a reliable measure of carbohydrate utilization is generally agreed, but that it is an accurate measure of

<sup>11</sup> Hari, P., and Halasz, A. V.: *Biochem. Z.* 1927, 19, 1.

<sup>12</sup> Carpenter, T. M.: *Human Metabolism*, 1927, p. 100.  
and Levitt, Washington, D. C., Carnegie Inst. 1927, 19, 1.



of determining the *absorption* of dextrose has been apparently well demonstrated. Furthermore, Brodie, Cullis and Halliburton<sup>13</sup> concluded from experiments in 1910 that increased consumption of oxygen might follow the introduction of ordinary distilled water into the bowel.

That the administration of dextrose to patients is not necessarily immediately followed by catabolism of this substance was shown by Koster and his associates.<sup>14</sup> They demonstrated that even when dextrose solutions were introduced directly into the blood stream the respiratory quotient was not altered if the injections were performed in the early days following an extensive surgical operation (the interpretation of this is that in such cases the injected dextrose is not rapidly and immediately catabolized).

*Results Obtained by the Direct Method.*—The direct or “wash-out” method would seem on first consideration to offer a rather easy solution to the problem.

1. Some of the early work in which this method of approach was used was done employing human beings and introducing the solution by anus.

Deucher<sup>15</sup> introduced 200 Gm. of dextrose into the rectum of a patient during a period of nineteen hours, after which he was able to recover only 46 Gm., or 23 per cent of the total amount.

Bingel<sup>16</sup> placed 35 Gm. of dextrose in the bowel of a series of diabetic patients and one hour later was able to recover 31 Gm. by washing out the colon.

Scott and Zweighaft<sup>17</sup> administered 10 to 30 per cent solutions of dextrose to medical students by rectum and recovered from 25 to 50 per cent.

The objections to these experimental observations are mainly three:

(a) Grossly hypertonic solutions were used, and hypertonicity probably hinders rather than facilitates absorption, as previously mentioned.

(b) Losses occurring as a result of unrecognized expulsion from the anus or regurgitation into the small intestine through the ileocecal valve would be falsely interpreted as due to colonic absorption.

(c) No allowance was made for the possible effect of dextrose-splitting bacteria or other dextrose-splitting agents in the bowel.

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13. Brodie, T. G.; Cullis, W. C., and Halliburton, W. D.: *J. Physiol.* **40**:173, 1910.

14. Koster, H.; Collens, W. S., and Goldzieher, M. A.: *Intravenous Injection of Glucose; Its Effect on Respiratory Quotient*, *Am. J. Surg.* **8**:970, 1930.

15. Deucher, P.: *Deutsches Arch. f. klin. Med.* **58**:210, 1897.

16. Bingel, A.: *Therap. d. Gegenw.* **46**:436, 1905.

17. Scott, E. L., and Zweighaft, J. F. B.: *Blood Sugar in Man Following the Rectal Administration of Dextrose*, *Arch. Int. Med.* **49**:221 (Feb.) 1932.

2. By far the most impressive experimental work has been performed on animals under anesthesia and after laparotomy.

McNealy and Willems<sup>18</sup> reported absorption experiments in a series of fifteen dogs prepared as follows: (a) All food was withheld for from sixteen to eighteen hours; (b) anesthetization was produced with barbitol and reenforced with a small amount of ether; (c) comparable loops of colon and ileum were isolated between ligatures, and glass cannulas were tied into the four ends of the isolated loops; (d) the isolated loops were thoroughly washed out with physiologic solution of sodium chloride, (e) from 50 to 75 cc. of 5 per cent dextrose solution was then introduced into each of the isolated loops; (f) the solutions were removed in toto by "washing-out" at the end of one-half hour; (g) similar amounts of 5 per cent dextrose solution were then introduced and washed out at the end of one hour, and (h) the solutions removed after one-half hour and one hour were then analyzed for sugar content. The venous blood draining from the loops was analyzed at the beginning and at the close of the observations.

The amount of dextrose lost from solutions introduced into the colon was small and within the limits of experimental error (from 3.4 per cent to 13 per cent); the amount of dextrose lost from the ileum was much greater (from 18 to 69 per cent). Analyses of the blood sugar level in the veins draining the isolated loops substantiated these conclusions, for in no case was there an appreciable increase of sugar in the blood draining from the colon, whereas in all cases there was a marked increase of sugar in the blood draining from the ileum.

Ebeling<sup>1</sup> used an experimental technic similar to that of McNealy and Willems. Dogs were used as experimental animals. Loops of intestine were isolated between ligatures at laparotomy under sodium amytal anesthesia, one loop consisting of the appendix and a segment of the adjacent ileum, and the other loop consisting of the colon and rectum. Glass cannulas were then tied into both ends of each loop. The intestinal segments were thoroughly flushed through and through with warm tap water. Measured amounts of warm 5 and 10 per cent solutions of pure lacto-dextrose were then introduced into the loops. Samples of blood were withdrawn from the femoral vein at intervals of one-half hour; samples of blood were taken from the ileal and colic veins before and after each period of observation. The sugar concentration was determined in every sample. At the end of each period of observation, the segments of intestine were thoroughly evacuated and flushed with 2500 cc. of distilled water. The percentage recovery of dextrose was calculated after chemical analysis.

<sup>18</sup> McNealy, R. W., and Willems, J. D.: Absorption of Glucose from Colon; Preliminary Study of Glucose Enema, Surg., Gynec. & Obst. 49:794, 1929.

Ebeling concluded from his observations on twenty-four animals:

(a) Solutions of dextrose are absorbed only slowly and in small amounts from the entire colon of the dog, but much more rapidly and in larger amounts from the ileum.

(b) The absorption of dextrose from a 10 per cent solution is slightly more rapid than that from a 5 per cent solution, but the difference in degree of absorption is not great.

(c) The rate and the amount of absorption of dextrose from the colon is much greater in hypoglycemic than in normal animals and in the former may approach the normal rate of absorption from the ileum.

(d) The blood sugar values show no direct correlation with the rate and the amount of intestinal absorption, especially when the latter is small.

(c) The water in a solution of dextrose is absorbed less rapidly by the colon than is tap water to which no dextrose has been added, i. e., the presence of dextrose hinders the absorption of water.

It seems on first consideration that the experiments of McNealy and Willems and Ebeling should definitely settle the question of colonic absorption. They found little absorption from the colon in a reasonably large and most carefully manipulated series of animals in which details of technic were carefully observed.

The only objections to complete acceptance of the findings are:

(a) What is found in a dog may not find direct application in man. This is an objection common to many experimental studies, and in this instance should probably carry little weight.

(b) The observations were made under anesthesia and after extensive intra-abdominal surgical manipulations. However, it should be remembered that these factors largely cancel out when absorption from the colon is compared with that from the ileum in the same animal at the same time.

(c) Absorption rates were compared based on segments of intestine which were apparently not measured with accuracy and which consequently may not have presented comparable surface areas. Obviously the unit of measurement which should be used as an index of absorption involves surface area and time; viz., a given portion of the intestinal mucosa absorbs at the rate of a certain number of cubic centimeters or grams of a given substance per unit area per unit of time. Any experiment which compares unknown surface areas yields results which may tell the truth or the direct opposite or any intermediate degree of truth or falsehood, depending on circumstances.

(d) The trauma to the intestine was maximal. Not only were loops of intestine brought out of the abdomen, isolated and ligated and

cannulas inserted, but they were then subjected to a thorough washing; therefore not only the outside or peritoneal coat was subjected to direct trauma but the mucosal surface as well. The effect of even slight trauma on the motility of the intestine is well known to all abdominal surgeons; mere opening of the abdomen causes cessation of practically all peristalsis, and the normal motility does not return for many hours after the abdomen has been carefully closed again. It seems reasonable to suppose that the absorptive function may suffer as great or even greater disturbance. If so, it would not seem mere wild conjecture to assume that different parts of the intestinal tract may show differential susceptibility. As a result of continued washing, the colon and rectum, which normally contain solid or semisolid material, may well undergo greater disturbance of absorptive function than the ileum, the contents of which are normally liquid. In this connection it should also be remembered that technically manipulation of the colon is more difficult and therefore more likely to be productive of trauma than is manipulation of the ileum, owing to the nature of its position and its attachments.

(e) The fact that under conditions of continued hypoglycemia Ebeling found the colon able to absorb dextrose nearly as well as the normal ileum certainly suggests that the colon is not lacking in ability to absorb.

#### EXPERIMENTS

The experiments about to be described were undertaken under the stimulation of the work of McNealy and Willems previously reviewed. They had already been completed before the appearance of Ebeling's excellent article. Had the results of these experiments agreed with those reported by McNealy and Willems and Ebeling, I should perhaps never have attempted to place them on record.

My work was undertaken, as already suggested, because of a conviction that all previous work not based on actual analysis of injected and recovered dextrose (the direct or "wash-out" method in experimental animals, in which all factors could be carefully controlled) was subject to so many discrepancies as well as differences of interpretation as to leave the question of colonic absorption practically unanswered. Furthermore, I felt that the work of McNealy and Willems, though highly suggestive of an answer, was not quite convincing, mainly because they allowed only a relatively short period of absorption after a period of intense trauma and then failed entirely to make their comparisons in terms of the amount of absorption per unit of surface area per unit of time.

Furthermore, inasmuch as these authors had used a barbituric acid derivative as an anesthetic agent and had then used blood sugar estimations as an essential part of their experimental observations without

investigating the effect of the drug itself on the blood sugar, it was felt that this matter should be subjected to observation.

Still further, in order to obviate, so far as possible, the factor of mucosal trauma due to repeated washings, I planned to allow absorption to occur in the presence of the normal intestinal contents; thus it became essential to determine the error introduced by the dextrolytic action of the normal contents.

Especially, I planned to allow a longer period of absorption—four hours instead of the one-half hour and one hour allowed by McNealy and Willems in order to reduce experimental error to a minimum.

The following technique was the common denominator of all of the experiments:

Presumably normal, full-grown mongrel dogs of various sizes were used as experimental material. Previous to the time of experimentation, the animals had been fed ordinary kennel rations. They underwent no period of preliminary fasting or other preliminary preparation of the intestinal tract. They were anesthetized by injecting into the external jugular vein a dose of sodium barbital computed on the basis of 0.3 Gm. of the drug per kilogram of body weight. Surgical anesthesia was induced by this dosage in most cases within from five to eight minutes. If at the end of ten minutes the animal was not entirely anesthetic, a small amount of ether was administered by inhalation to the point of anesthesia. The animal's abdomen was then opened by means of a 2 or 3 inch (about 5 or 7 cm.) low paramedian incision.

Specifically, the experiments were divided into four series, which were planned to answer the following questions:

1. To what extent are the normal contents of the ileum and colon capable of splitting artificially prepared dextrose solutions when acting at body temperature for a given interval of time?

2. Does sodium barbital in anesthetic doses itself have an effect on the blood sugar?

3. Do laparotomy and extensive intra-abdominal manipulation have an effect on the blood sugar?

4. To what extent do the various parts of the intestine absorb dextrose and water from isotonic and hypertonic dextrose solutions?

*Lysis of Artificially Prepared Dextrose Solutions by Intestinal Contents.*—Five dogs were used. The entire colon and rectum were isolated between ligatures after the mesenteric blood supply was controlled. A corresponding segment of the terminal portion (about 40 cm.) of the ileum was isolated between ligatures and removed in the same manner. The content of each of these segments was then expressed into a separate beaker. Exactly 150 cc. of an accurately prepared 5 per cent solution of bacto-dextrose solution was then added to each of the two solutions. The beakers were placed in the incubator at 37.5 C. for four hours. The solutions were then carefully filtered, measured and

analyzed by Benedict's quantitative urinary sugar method for dextrose content. The loss of dextrose was calculated.

Results: Both colonic and ileal contents showed dextrolytic properties, but the colonic contents showed more active lytic properties than the ileal contents. The average recoveries were as follows: for the colon, recovery of 87 per cent of the added dextrose; for the ileum, recovery of 96.6 per cent of the added dextrose.

There is little opportunity for direct comparison between these results and the results obtained by previous investigators, for the experimental conditions have not been comparable.

Bingel<sup>19</sup> found that when dextrose was added to fecal material and incubated the loss was almost as great as that which occurred when dextrose was placed in the bowel of a living diabetic patient.

Boyd and Robertson<sup>20</sup> incubated dextrose solutions with colon bacilli and concluded that the amount of dextrose disappearing as a result of bacterial action was insignificant.

In 1925, Cori<sup>21</sup> incubated measured quantities of dextrose in segments of the small intestine at 37 C. for periods of from three to five hours, and concluded that the loss of dextrose due to bacterial action was so small as to be negligible.

Pressman<sup>6</sup> found that nearly 90 per cent of the dextrose in a given solution was destroyed by incubation with feces for seven hours.

Ebeling<sup>1</sup> incubated 75 cc. of a 4.7 per cent solution of dextrose in an excised and washed segment of the colon at 37.5 C. for two hours and estimated the loss of dextrose as a result of the incubation at 2.6 per cent.

*Effect of Anesthetic Doses of Sodium Barbitol on Blood Sugar.*—In a series of twenty dogs Folin and Wu blood sugar analyses were performed: (1) just before the administration of anesthetic doses of sodium barbitol and (2) again about five minutes after surgical anesthesia had been induced by this drug.

Results: Fifteen of the twenty dogs, or 75 per cent, reacted with a relative hyperglycemia. The increase varied between 2.5 mg. and 50.1 mg. per hundred cubic centimeters, with an average of 15.46 mg.

The remaining five animals reacted with a relative hypoglycemia and showed decrements ranging between 1.1 mg. and 9.5 mg. per hundred cubic centimeters, with an average of 6.24 mg.

From these findings it becomes evident that pharmacologically sodium barbitol belongs to a group of drugs which in toxic doses characteristically produce hyperglycemia; included in this group are epinephrine,

19. Bingel, A.: *Therap. d. Gegenw.* **46**:436, 1905.

20. Boyd, F. D., and Robertson, T.: *Scottish M. & S. J.* **18**:193, 1906.

21. Cori, C. F.: Fate of Sugar in Animal Body; Rate of Absorption of Hexoses and Pentoses from Intestinal Tract, *J. Biol. Chem.* **66**:691, 1925.

picrotoxin, quinine and probably many others. The exact mechanism by which this particular drug produces its hyperglycemic effect can be determined only by further experimentation, as the hyperglycemic mechanism does not seem to be the same for all drugs.

This interesting pharmacologic observation is not recorded with the purpose of suggesting that false conclusions have necessarily been drawn when experimental work has been performed under the anesthetic action of the barbiturates; not only may other barbiturates, like amytal, fail to show this action, but presumably a normal blood sugar reading has been made after the administration of the drug. However, the possibility of serious error is suggested, and the phenomenon can at least be cited as evidence of the general instability of the blood sugar under experimental conditions.

*Effect of Laparotomy and Intra-Abdominal Manipulation on the Blood Sugar.*—In a series of seventeen dogs surgically anesthetized with sodium barbital the effect on the blood sugar of laparotomy and intra-abdominal manipulations was studied as follows:

Folin and Wu blood sugar determinations after anesthetization with sodium barbital were compared with a similar series of blood sugar determinations made after the abdomen had been opened and the colon and ileum had been ligated and cannulas tied in, as will be described in the discussion of the principal part of the experiment, which follows.

Results: All except two of the seventeen animals, i. e., 88 per cent, showed relative hyperglycemia as a result of the operative manipulations. The increases varied between 13.4 mg. and 92.7 mg. per hundred cubic centimeters, with an average of 39.36 mg.

The two animals excepted showed decrements of 12.9 mg. and 2.5 mg. per hundred cubic centimeters, respectively.

These results introduce the opportunity for rather interesting speculation as to the general value of blood sugar estimations as a measure of intestinal absorption under traumatic experimental conditions. If the peripheral blood sugar varies so greatly as a result of mechanical surgical manipulation alone, how can one hope to settle the question of intestinal absorption by a study at least of portal blood sugar values, since the mere obtaining of samples of blood for the determinations is inevitably associated with rather extensive handling of the intra-abdominal organs?

*Differential Absorption of Dextrose and Water by the Colon, Ileum and Jejunum.*—The "wash-out" method in combination with periodic examinations of the peripheral blood sugar was used in an attempt to determine the differential absorption of dextrose and water by the colon, ileum and jejunum.

A series of twenty dogs formed the basis for the conclusions; other animals were used but were not included in the final compilation of results because they did not yield a complete series of observations.

After the induction of anesthesia and the performance of laparotomy, as previously described, segments of intestine were isolated between tightly tied ligatures. Cannulas were inserted into these segments proximally only; the technic of inserting the cannulas consisted of (1) the introduction of a purse-string suture of linen just distal to the point of proximal ligation, (2) the introduction of a small glass cannula through the purse-string suture about the cannula (the purse-string suture was then tightly drawn) and (3) the introduction and tying of a second concentrically placed purse-string suture so as to preclude all possibility of leakage. The cannula was then connected by a short piece of rubber tubing to a short buret of large bore (50 cc. syringe barrel). The buret was held in a vertical position just above the animal's abdomen by means of a buret clamp. All of the manipulations were performed as rapidly and with as little trauma as possible; laparotomy pads wet with warm saline solution were freely used, and the greatest care was taken to prevent chilling of the abdominal contents and undue exposure to the air. As soon as these relatively simple manipulations had been made, the abdominal incisions were closed by means of several interrupted "through and through" sutures, and the animals were not disturbed thereafter for the duration of the experiment except periodically to withdraw blood from the external jugular vein.

The animals were prepared in two series of ten animals each. In one series 10 per cent solutions of dextrose were used; in the other, 5 per cent solutions of dextrose were used. Bacto-dextrose was employed for the preparation of solutions throughout; the dextrose was accurately weighed on a good analytic balance, and the solutions were subsequently checked by titration.

In five animals in each series as much of the colon as could be isolated intra-abdominally was used for one loop, and a corresponding length of the lowest part of the ileum (about 40 cm.) was used for a second loop; the cecal appendage was not included in either loop. In the other five animals of each series a third loop consisting of a comparable portion of jejunum was also isolated. Thus, in five animals of each series two loops (colon and ileum) were used, and in the remaining five animals three loops (colon, ileum and jejunum) were used.

The experimental observations began as soon as the abdomen of each animal was closed and the burets attached. First a sample consisting of 5 cc. of blood was obtained from the external jugular vein. Then an accurately measured amount of dextrose solution was poured into each buret. At intervals of exactly one hour additional samples of blood were removed from the external jugular vein. The fluid level in the burets was maintained, as absorption occurred, by the addition of measured amounts of dextrose solution; thus variable but accurately measured amounts were introduced, depending on the capacity and absorptive reaction of the individual loop. At the end of four hours, the animals were killed, the abdomen was rapidly opened, the loops of intestine were cut away, the contents of the loops were carefully collected and measured, and the loops were carefully split longitudinally and their surface areas computed by mensuration.

All of the blood samples were immediately analyzed for sugar content by the method of Folin and Wu for blood sugar. All of the fluid collected from the intestinal loops was immediately measured, filtered through coarse filter paper and analyzed for sugar content by Benedict's method for urinary sugar.



Results: The amounts of water absorbed by the mucosa per hundred square centimeters of surface area per hour are revealed in table 1; each computation represents the average of ten observations for the colon and the ileum and five observations for the jejunum.

It is obvious that all portions of the intestinal tract (colon, ileum and jejunum) absorb water from both 5 per cent (isotonic) and 10 per cent (hypertonic) solutions of dextrose. From the 5 per cent or isotonic solution, however, relatively large quantities of water are absorbed, whereas from the 10 per cent or hypertonic solution much smaller quantities are withdrawn.

TABLE 1.—*Mucosal Absorption of Water from Aqueous Solutions of Dextrose*

Solution of Dextrose	Cubic Centimeters of Water Absorbed per Hour per Square Centimeter of Surface Area of Mucosa		
	Colon	Ileum	Jejunum
5%	11.46	6.18	26.36
10%	8.5	0.15	1.8

TABLE 2.—*Absorption of Dextrose*

Solution of Dextrose	Segment Absorbing	Grams of Dextrose Absorbed per Hour per Hundred Square Centimeters of Mucosal Surface Area		
		Colon	Ileum	Jejunum
5%	Colon and Ileum.....	1.93	1.66	
	Colon, Ileum and jejunum.....	1.36	0.55	159.0
10%	Colon and Ileum.....	1.12	1.02	
	Colon, Ileum and jejunum.....	0.95	0.78	165.0

Although the jejunum absorbs water freely and in large quantities from a 5 per cent solution, it takes relatively little from a 10 per cent solution. The ileum absorbs considerably less water than the colon from both 5 per cent and 10 per cent solutions of dextrose; from the 10 per cent solution the ileum absorbs water scarcely at all. The colon absorbs less than half as much water as the jejunum from a 5 per cent solution of dextrose but more than four times as much from a 10 per cent solution.

The quantities of dextrose absorbed by the mucosa per hour per hundred square centimeters of surface area are recorded in table 2. The figures are uncorrected for the dextrolytic action of the intestinal contents. If they are corrected according to the percentages obtained in the preceding preliminary experiments (incubation experiments), the results indicated in table 3 are obtained.

It is evident from these computations that the jejunum absorbs vastly more dextrose from 5 and 10 per cent solutions than does the colon

or the ileum; the jejunum, however, absorbs only insignificantly more dextrose from a 10 per cent solution than it does from a 5 per cent solution. The colon and ileum absorb dextrose from 5 and 10 per cent solutions, but they absorb less from a 10 per cent solution than from a 5 per cent solution. The absorptive powers of the colon and ileum for dextrose are practically equal, though the figures show that the colon absorbs somewhat more than the ileum; previous investigators had found that it absorbed less.

The peripheral blood sugar values are given in table 4. They tend to fluctuate as a function of the amount of intestinal absorption.

TABLE 3.—*Figures in Table 2 Corrected for the Dextrolytic Action of the Intestinal Contents*

Solution of Dextrose	Segment Absorbing	Colon	Ileum
5%	Colon and ileum.....	1.65	1.60
	Colon, ileum and jejunum.....	1.15	0.53
10%	Colon and ileum.....	0.98	0.98
	Colon, ileum and jejunum.....	0.55	0.75

TABLE 4.—*The Peripheral Blood Sugar Values During Active Absorption of Dextrose from Colon, Ileum and Jejunum*

Solution of Dextrose	Segment Absorbing	Milligrams of Sugar per Hundred Cubic Centimeters— An Average of 10 Observations			
		After 1st Hour	After 2d Hour	After 3d Hour	After 4th Hour
5%	Colon and ileum.....	143.0	151.7	143.3	121.2
	Colon, ileum and jejunum.....	165.0	155.7	190.3	181.8
10%	Colon and ileum.....	160.4	164.5	167.9	167.9
	Colon, ileum and jejunum.....	156.2	208.1	238.2	262.3

In all of the cases, at the end of one hour of intestinal absorption the peripheral blood sugar had increased significantly.

A consistently greater increase in peripheral blood sugar occurred when the colon, ileum and jejunum were absorbing than when only the colon and ileum were absorbing, as would be expected from the previously demonstrated relatively enormous absorptive power of the jejunum. This was true with respect to both 5 and 10 per cent solutions.

That the intestinal absorption of dextrose and the increase in the peripheral blood sugar do not vary in exact parallelism, however, is suggested by the fact that the blood sugar when computed for four hours does not show consistent increments from hour to hour, but rather shows fluctuations and at times even decreases. Conceivably in the cases in which decrements occur intestinal absorption may have been halted for some unknown reason, but it seems more reasonable to believe that

the variations represent the interplay of other factors which would vitiate the general parallelism between absorption and the increase in the peripheral blood sugar.

#### COMMENT

In view of the relative facility with which the colon absorbs water and, according to these experimental findings at least, dextrose as well, the prejudice which many surgeons have come to have against proctoclysis as a clinical method is not altogether easy to understand.

In the human adult the large intestine exclusive of the rectum and the anal canal is from 135 to 140 cm. in length and presents an average diameter of about 5 cm. or more; accordingly, a conservative estimate of its mucosal surface area on the basis of these figures is 2,110 square centimeters. Assuming that the human colon absorbs at the same rate as that of the dog, it is capable, according to the present experimental findings, of absorbing about 240 cc. of water and 30 Gm. of dextrose per hour from a proctoclysis of 5 per cent dextrose solution. These figures are conservative, and they do not include such absorption as might occur from the rectum.

Many persons, of course, are unsuccessful in the use of proctoclysis because in their adaptation of apparatus and solutions they disregard fundamental physiologic principles. If too large a retention enema is given it produces discomfort or actual pain and is likely to be expelled rather promptly. Similarly, when a "drip" proctoclysis is used if the receptacle used as a reservoir is placed more than about 18 inches (about 40 cm.) above the level of the anus and the solution is allowed to flow into the bowel more rapidly than it can be absorbed, an incompatible amount of pressure is likely to develop within the colon, and the medical attendant is likely to find a leakage of solution about the rectal tube into the bed.

Probably the most fruitful source of difficulty, however, arises from the use of hypertonic solutions; as these experiments indicate, such solutions are inimical rather than conducive to absorption of water or dextrose. They undoubtedly tend by osmosis to withdraw fluid from the tissues; not only does this produce an effect diametrically opposite to the one desired, but the tissue fluid augments the bulk of the solution in the bowel, and the mere bulk is apt to stimulate expulsive efforts.

#### SUMMARY

1. The opinion that dextrose is absorbed only slightly, if at all, by the colon does not seem to be well supported by experimental evidence.
2. Much of the confusion in experimental results in the past has arisen from the fact that hypertonic solutions have been commonly used; the primary action of such solutions is probably an osmotic one according

to which water is withdrawn from the intestine and progressively dilutes the solution. From a practical point of view the outpouring of water is apt to increase the bulk of the solution to such an extent that the intestine is stimulated to expulsive movements. Such absorption of dextrose as does occur before isotonicity is established, i. e., from a hypertonic solution, must occur selectively and against osmosis.

3. Little dependence can be placed on experiments based on the assumption that the blood sugar level rises proportionately with the amount of intestinal absorption of dextrose. The parallelism may or may not exist, according to circumstances. The blood sugar level should be considered as a variable which is in a continuous state of flux and which is determined by the interplay of many different factors. Two factors previously ignored, which under experimental conditions, at least, may exert a profound hyperglycemic influence have been examined, and it has been found that:

(a) The general blood sugar level is elevated in more than three quarters of the cases by the administration of sodium barbital in doses sufficient to produce surgical anesthesia.

(b) Surgical manipulations also heighten the general blood sugar level in more than three quarters of the cases.

Variations of the local portal blood sugar, i. e., the blood sugar in the area draining loops of intestine which are actively absorbing dextrose solutions, are very likely of even less significance than the variations in the systemic blood sugar and this for a simple and obvious reason. Under the given conditions the coil of intestine absorbs dextrose and water, the dextrose being in solution in the water. If the local blood stream happens to absorb dextrose and water from the solution in a certain proportion each to each, i. e., in the proportion in which they exist in the blood at that point and if all other factors remain constant, it is obvious that no change occurs in the blood sugar concentration in spite of the absorption of the dextrose. On the other hand, at other differential absorption rates, the blood sugar might appear to decrease while actually increasing or might appear to increase while actually decreasing, depending entirely on whether the direction of the migration of the water is into or out of the intestine.

Accepting the apparently demonstrated fact that the colon absorbs water much more readily and rapidly than the ileum, the effect of this differential absorption would be to mask colonic absorption of dextrose and magnify the absorptive action of the ileum.

4. The respiratory quotient is an accepted measure of the utilization of dextrose, but no dependence can be placed on the respiratory quotient as a measure of intestinal absorption of dextrose. Consequently, con-

clusions based on variations of the respiratory quotient can be dismissed summarily as valueless.

5. Conclusions as to colonic absorption based on analyses of dextrose solutions first introduced into the intact intestinal canal through the rectum and then recovered by the same avenue are unreliable for two reasons: (*a*) It is probably impossible to control regurgitation of such solutions through the ileocecal valve and difficult absolutely to prevent regurgitation through the anus, thus preventing all loss not due to absorption, and (*b*) the factor of lysis by intestinal contents at body temperature is disregarded.

6. Although previous experiments using much the same technic as that used in the experiments herewith reported have seemed to show that the colon absorbs little dextrose in comparison with the ileum, I have been able to demonstrate, (*a*) by reducing trauma to an absolute minimum, (*b*) by using a relatively long period of observation and (*c*) most important of all, by comparing accurately measured equal areas of intestinal mucosa, that the colon absorbs dextrose as actively as the ileum and water in far larger amounts.

7. The present series of experiments indicates that the use by rectum of a hypertonic solution of dextrose is highly undesirable. From a 10 per cent solution, actually less dextrose is absorbed by the lower part of the intestinal tract than from a 5 per cent (practically isotonic) solution, and the hypertonic solution interferes markedly with the absorption of water as well.

8. Although, according to the present experiments, the lower portion of the intestinal tract under favorable conditions is capable of absorbing considerable quantities of dextrose and water, and although proctoclysis can therefore be regarded as of definite clinical value, the amount of absorption of dextrose which occurs low in the intestinal tract is only a fraction of that which occurs in the jejunum. Rectal administration of dextrose is therefore only a relatively inefficient substitute for oral administration and should be adopted only when, for one reason or another, oral administration is contraindicated.

# THE VISCEROSPINAL SYNDROME: A CONFUSING FACTOR IN SURGICAL DIAGNOSIS

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In presenting this subject we realize that we are adding to the already voluminous writings on pseudopathology which have accumulated through the years, and we are fully aware of the futility of any presentation which is merely an addition to the store. However, if by the presentation of certain clinical observations we can stimulate discussion and further active investigation in a field which despite the literature is still somewhat uncharted, a definite contribution will have been made.

In the diagnosis of surgical conditions, acute or chronic, involving the viscera we are usually confronted with certain signs and symptoms which we consider characteristic. Pain, tenderness, nausea and vomiting, abdominal rigidity and distention comprise a chain which surgeons are prone to interpret as signifying pathologic involvement of the viscera. The fact that conditions remote from the apparent location of the disturbance—extravisceral conditions, let us say—may produce signs similar to those of pathologic involvement of the viscera is not always given due consideration.

Our attention was recently drawn to this subject by one of our associates, N. T. Ussher, who for a number of years has studied the relationship between certain chronic visceral disturbances and spinal curvatures. In a recent article Ussher,<sup>1</sup> following a careful search of the literature, made the interesting observation that the effect of certain skeletal abnormalities on the viscera is not generally recognized.

True, a number of writers, notably Dejerine,<sup>2</sup> Carnett,<sup>3</sup> Gunther and

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Read before the section on general surgery at the Sixty-Second Annual Session of the California Medical Association, Del Monte, Calif., April 24, 1933.

1. Ussher, N. T.: Spinal Curvatures—Visceral Disturbances in Relation Thereto, California & West. Med. **38**:423 (June) 1933.

2. Dejerine, J.: *Semiologie des affections du système nerveux*, Paris, Masson & Cie, 1914, p. 257.

3. Carnett, J. B.: The Simulation of Gall-Bladder Disease by Intercostal Neuralgia of the Abdominal Wall, Ann. Surg. **86**:747 (Nov.) 1927; Chronic Pseudoappendicitis Due to Intercostal Neuralgia, Am. J. M. Sc. **174**:579 (Nov.) 1927.

Kerr,<sup>1</sup> Nielsen<sup>5</sup> and others,<sup>6</sup> have repeatedly described syndromes due to pathologic changes in the nerve roots or trunks (at or near the spine), the chief symptoms of which have been pain and hyperesthesia of some area remote from the source. The cases reported have usually been classified as radiculitis, the radicular syndrome and intercostal neuralgia.

On careful study of about fifty cases which appeared to be caused by some derangement at or near the spine or involving the nerves of this region Ussher noted that the disturbances were not the simple peripheral nerve conditions which had been previously described but that they showed symptoms distinctly visceral as well. He has suggested the term "viscero-spinal syndrome" as describing their origin and its bearing on their symptomatology.

In the past few years there have been considerable speculation and a large amount of investigative work on the relationship of the somatic to the visceral nervous system<sup>7</sup> from the standpoint of referred pain, tenderness and muscular rigidity, and several interesting theories have been propounded.

To go into all the details or to weigh the merits and demerits of the several theories at this time would avail us little since the various investigators<sup>8</sup> in no wise agree as to the mechanism involved. That there is a definite relationship between the viscera and the corresponding segmental distribution of nerves is held by Pottenger<sup>9</sup> who stated: "The segmental relationship which exists between an efferent visceral neuron and an afferent somatic neuron probably also exists between an afferent somatic and an efferent visceral neuron." He suggested that

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4. Gunther, Lewis, and Kerr, W. J.: The Radicular Syndrome in Hypertrophic Osteo-Arthritis of the Spine: An Analysis of Thirty Cases, *Arch. Int. Med.* **43**:212 (Feb.) 1929.

5. Nielsen, J. M.: The Radicular Syndrome, *J. A. M. A.* **88**:1623 (May 21) 1927.

6. Mayer, E. E.: Radiculitis: Its Diagnosis and Interpretation, *J. A. M. A.* **71**:353 (Aug. 3) 1918.

7. Morley, J.: Significance of Afferent Impulses from the Skin in the Mechanism of Abdominal Pain, *Lancet* **2**:1240 (Dec. 14) 1929. Robertson, George: Disturbed Reflexes; Their Significance in Acute Abdominal Disease, *Surg., Gynec. & Obst.* **43**:807 (Dec.) 1926.

8. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin in the Mechanism of Visceral Pain, *Am. J. M. Sc.* **176**:517 (Oct.) 1928. Forbes, A.; Cannon, W. B.; O'Connor, J.; Hopkins, A. McH., and Miller, R. H.: Muscular Rigidity With and Without Sympathetic Innervation, *Arch. Surg.* **13**:303 (Sept.) 1926. Livingston, E. M.: The Skin Triangle of Appendicitis, *Arch. Surg.* **13**:631 (Nov.) 1926.

9. Pottenger, F. M.: Important Reflex Relationships Between the Lungs and Other Viscera, *J. Thoracic Surg.* **1**:75 (Oct.) 1931.

"there is a continuous flow of stimuli from the surface of the body inward to the viscera and from the viscera outward to the skeletal tissues."

Assuming for the moment that this relation exists, is it unreasonable to suggest that apparent visceral symptoms may have as their origin stimuli due to pathologic changes somewhere in the surface or skeletal structures? Is it unreasonable further to assume that, given a strong enough stimulus from some more remote region, actual disturbance in the visceral physiology could be brought about?

Let us consider for a moment an injury such as a strain of the muscles of the lumbar and dorsal region in which a few strands or fibers are torn. A traumatic myositis is set up with spasticity of the muscle. There may be little or no pain on ordinary movement, for, as Hoover<sup>10</sup> stated, unlike inflammation of other structures of the body, inflammation of a muscle is relatively painless on activation, providing the sheath or tendon is not involved.

This spasm sets up a reflex spasm in the abdominal musculature whether for the purpose of splinting the weakened back as suggested by some writers or for some other reason.

It is conceivable that irritation of the afferent neurons of this damaged muscle, depending on the location and extent of the damage, might be responsible for transmission of stimuli via one of the reflex pathways to the viscera, and that symptoms of nausea and vomiting, pain and distention might appear. The chain of symptoms thus produced might so exactly simulate those of actual visceral disease as to make the diagnosis of the true condition extremely difficult.

We are sure that the first reaction to such a glib statement of what is necessarily a complex mechanism will be to demand a proof of what is admittedly a rather amazing assumption.

Unfortunately, when dealing with a subject in which so little is known and so much is still speculation conclusive proof may be extremely difficult.

At the present time the experimental evidence concerning sympathetic and parasympathetic reflex mechanisms is somewhat confused, and we believe that in the light of present knowledge an adequate explanation of the phenomena which we have observed clinically cannot be reconciled with existing theories.

At the outset of this article we stated that we wished to present clinical data based on observation in the hope of stimulating further investigation. We shall present the histories of a few cases illustrating this syndrome.

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10. Hoover, C. F.: Diseases of the Muscles, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Co., Inc., 1920, p. 527.



## REPORT OF CASES

CASE 1.—A man, single, white, aged 39 years, was referred to our service with a tentative diagnosis of acute appendicitis. The patient stated that while pitching hay the day before the onset he felt a "catch" in his back which hurt him somewhat on lifting during the rest of the afternoon. The following morning at 5 a. m. he awoke with severe cramplike pain over the entire abdomen; the pain later localized in both lower quadrants. On admission the duration of this pain was ten hours.

Nausea and vomiting came on about one hour after the onset and persisted intermittently up to the time of admission. There was no bowel movement until late in the afternoon when a small amount was passed. The pain was increasingly severe on moving about.

*Examination.*—The examination revealed a well developed white man lying with knees drawn up, apparently in considerable pain. The head, neck and chest were normal. The temperature was 98 F., the pulse rate, 60; the respiratory rate, 20.

Abdomen: There was marked boardlike rigidity of the lower part of the abdomen. The right lower quadrant was tender on pressure. The kidneys were not palpable.

The lumbar and dorsal muscles were spastic and extremely tender on pressure.

*Laboratory Examination.*—The white cell count was 9,000 with 80 per cent polymorphonuclear leukocytes. The urine was normal; the Wassermann and Kahn reactions were negative.

*Treatment.*—Heat was applied to the dorsolumbar region and heavy strapping for support.

*Progress.*—The pain in the abdomen subsided rapidly; there was no further nausea or vomiting, and rigidity disappeared within twelve hours. The pain shifted to the thigh and down to the knees. The patient rapidly improved and left the hospital in a few days with no other complaint than that of slight tenderness in the back.

CASE 2.—W. C. F., a married man, aged 39, a plumber, had been perfectly well until the day before entrance when on lifting a heavy laundry tray he experienced a sharp pain in the lower part of the abdomen. The pain seemed to encircle the lower part of the abdomen and the back. Occasionally it was more severe in the right flank and radiated down the inner side of the right thigh. The pain in the lower part of the abdomen was continuous. He was seen in our office by the orthopedist who made a diagnosis of traumatic lumbar myositis. The patient received heat and massage to the dorsolumbar region. He stated that the muscles of his back were "tied in a knot." The pain became worse on walking home. During the day and night there were many attacks of colicky pain localized in the right flank, and that evening the patient was nauseated and vomited two or three times. These attacks were accompanied by writhing on the bed, profuse perspiration and almost uncontrollable pain. There was no urgency, frequency or other urinary symptoms.

*Examination.*—An examination made at 4 a. m. gave negative results except for the back and abdomen.

Back: The back presented bilateral muscular spasm, in which the lumbar muscles were extremely hard, tense, tender and painful.

Abdomen: The abdomen showed absolute boardlike rigidity, increased tenderness in the right flank, colicky spasms of pain localized on the right side in

both upper and lower quadrants and pain down the inner side of the right thigh. There were no palpable masses and no rebound tenderness; the abdomen was tympanitic throughout.

*Laboratory Examination.*—The urine was normal except for occasional red blood cells. A later specimen of urine showed a trace of sugar and a trace of albumin with no red blood cells. The white cell count was 10,800 with 88 per cent polymorphonuclears. A later count showed 10,900 white cells with 80 per cent polymorphonuclears.

The roentgenographic study revealed no shadow in the region of the kidneys or ureters. Careful straining of the urine disclosed no calculi.

*Progress.*—After a discussion of the probable diagnosis a seven strap support was applied to the dorsolumbar and lumbar regions, a small dose of morphine administered, and the patient put in a semi-Fowler position with the knees elevated to relax the lumbar muscles. When he awoke from the narcosis the colicky pain was entirely relieved, and the pain in the back was diminished. He was discharged from the hospital on the second day and after adequate physical therapy made a complete recovery. At the time of writing, one year after the attack, there had been no recurrence.

*CASE 3.*—A white man, married, aged 48, was brought into the office complaining of severe cramplike pain in the lower part of the abdomen, nausea, vomiting and loss of appetite. He stated that the first attack came on two weeks previously and that he was awakened out of sleep. He had been moving some heavy farm machinery the day before and had strained his back. He stated that he vomited once on the day of the onset and that the abdominal pain was so severe that he was forced to remain in bed several days. Subsequently he improved somewhat and was able to be up and about, but on the day before admission while he was at work the pain and nausea returned. He had a poor appetite during the entire two weeks, and the bowels were sluggish.

*Examination.*—The examination revealed a small moderately well developed white man. The head, neck and chest were normal. The temperature was 98.6 F., the pulse rate, 70; the respiratory rate, 18. The abdomen was markedly rigid in both lower quadrants and moderately rigid in the upper part. There was tenderness in the right lower quadrant. Marked spasm and tenderness on pressure were noted over the right lumbar and right lower dorsal region. The patient could not stand up straight.

*Laboratory Examination.*—The white cell count was 6,000 with 65 per cent polymorphonuclears. The urine was normal, and the Wassermann and Kahn reactions were negative.

*Treatment.*—Application of heat to the dorsolumbar region and a tight back strapping were followed by relief from the abdominal pain in one hour. Further treatment with heat and massage was followed by complete recovery.

*CASE 4.*—A white truck driver, married, aged 26, was referred to our service complaining of intermittent pain in the left flank radiating to the back and lower part of the abdomen. The patient stated that the pain was always worse after he walked or rode in a truck. Usually he felt well on rising, but after he got about the pain came on increasingly as the day wore on. Nausea occurred frequently during attacks of pain. He had lost 20 pounds (9.1 Kg.). The duration of the condition was two and one-half years in which he had made the rounds of physicians and cultists with no relief.

*Examination.*—The examination revealed tenderness high in the left lumbar region and in the lower left quadrant of the abdomen on deep pressure. The abdominal muscles were slightly rigid. The left kidney was not palpable. A cystoscopic examination showed that the mucosa of the bladder was normal. The left ureter was catheterized with difficulty using a number 4 (French) catheter. The urine gave negative results culturally. No evidence of tuberculosis was seen, and inoculation of guinea-pigs gave negative results. Pyelograms showed the kidney to be in normal position; no abnormality was seen. Filling of the renal pelvis reproduced the pain (voluntary statement) but more severe than ordinarily. A diagnosis of stricture of the ureter was made.

*Treatment.*—Dilation of the left ureter at first gave relief for a day or so; later these treatments were of no benefit even after dilation with a number 12 catheter. On recheck examination a number 5 catheter was passed and ascended with resistance. Attempts to withdraw it revealed that it was in the grip of a spastic ureter.

The patient was referred to the orthopedic department for a check up. Examination showed a spastic left dorsolumbar region with tenderness of the muscles on pressure and a short left leg. There was a moderate scoliosis. The heel was raised one-fourth inch (0.64 cm.), and muscle training was given. The pain left within a few hours, and within two weeks the patient could walk several miles without discomfort. The appetite returned and the patient regained 5 pounds (2.3 Kg.) in the first month. Two and one-half months later he was working and free from pain. The only recurrence he has had took place one day when he wore his old work shoes on which there was no heel correction.

CASE 5.—A white man, aged 31, was seen at the office complaining of attacks of pain radiating along the third and fourth ribs on the right side, discomfort on motoring due to a tired back, vague abdominal distress, vomiting and gas in the intestines near the stomach. These attacks had occurred intermittently for ten years. Roentgenograms of the gastro-intestinal tract were negative. An appendectomy in which an essentially normal appendix was removed because of pain and hyperesthesia in the lower right quadrant gave no relief. Two years later symptoms of mild ureteral colic developed on the right side. These persisted from two to three weeks. A cystoscopic examination gave negative results except for a slight angulation of the right ureter slightly below the right kidney. The patient had come to Santa Barbara for his health three or four years before.

On examination by our orthopedist he was found to have a dorsal scoliosis and a short right leg. The right heel was raised one-fourth inch and muscle training was given, which relieved the abdominal symptoms in two weeks; all distress ceased in a month. One year later there was a mild recurrence, but the raising of the heel an additional one-fourth inch and more vigorous muscle training cleared up the symptoms satisfactorily. Recently when playing golf, wearing a new pair of shoes without the raised heel, the patient had a recurrence of the abdominal symptoms, which responded immediately to the correction.

#### COMMENT

The cases here presented are a few of the typical ones in the series studied; we believe that they illustrate definite visceral disturbances resulting from stimuli arising outside of the viscera themselves.

It is our belief that the mechanism of production of these symptoms is essentially the same whether they follow direct trauma due to sudden

straining of the back or result from the chronic strain due to scolioses or other spinal curvatures. Hoover, in his discussion of myositis, stated that ordinary stretching of a muscle is not necessarily productive of local pain but that continuation of the stretching produces an area painful and tender to pressure—a definite myositis. We stress the dorsal and lumbar myositis because this appears to be the common factor in our series, and while the fact may be merely coincidental, following therapy directed at correction of the myositis the symptoms in every case cleared up.

We believe that this group of cases does not fall into the group classified as intercostal neuralgias as they are at present understood, since according to Carnett and others who have written extensively on pseudo-appendicitis and pseudo-disease of the gallbladder intercostal neuralgias should be ruled out when rigidity of the abdomen and actual visceral disturbances are noted.

We believe that we have been able to rule out the psychalgias<sup>11</sup> in the cases studied. This seems particularly true in the last two cases reported.

We are not prepared at this time to say that these symptoms may be explained on the basis of a radiculitis. The early, at times almost spectacular, relief that follows physical therapeutic measures seems to speak against pathologic changes in the nerve roots as a causative factor. Further, if the myositis which was invariably present is a responsible factor, it directs attention toward the endings rather than toward the roots or trunks of the nerves.

We do not wish to have it understood that we regard conditions in the back as in any way productive of pathologic changes of the viscera, but basing our assumption on our observations we feel safe in concluding that there is most certainly a disturbance of the physiologic processes. Neither do we suggest that surgical intervention be always withheld in questionable cases pending orthopedic checking and physical therapy, as we all know that the delay may be disastrous when actual pathologic changes are present and present an atypical symptomatology. We are taught by various writers<sup>12</sup> on abdominal diagnosis that pain lasting over a period of six hours together with nausea and vomiting and a rigid tender abdomen usually denotes pathologic changes in the viscera. It is not the purpose of this article to deny the truth of that

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11. Pratt, J. H.; Golden, L. A., and Rosenthal, J.: *The Psychalgias*, J. A. M. A. 98:441 (Feb. 6) 1932.

12. Cope, Zachary: *The Early Diagnosis of the Acute Abdomen*, New York, Oxford University Press, 1928. MacKenzie, J.: *Symptoms and Their Interpretations*, ed. 4, London, Shaw & Sons, Ltd., 1920.

dictum but rather to correct a more or less rule of thumb that "usually" means "always."

Finally to those who, like ourselves, after carefully evaluating a chain of symptoms, have opened an abdomen and removed an unoffending appendix, performed a fixation on an innocent if malposed kidney, repeatedly dilated an apparently strictured ureter or explored and found a normal gallbladder we wish to offer what appears to us a plausible reason for the symptoms in a few of these cases.

Santa Barbara Clinic.

# OBSTRUCTION OF THE SUPERIOR VENA CAVA

## AN EXPERIMENTAL STUDY

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The clinical features of obstruction of the superior vena cava have been discussed by Ehrlich, Ballon and Graham.<sup>1</sup> As a review of the literature revealed no references to experimental studies of this condition in laboratory animals, a series of experiments were undertaken in which the superior vena cava was obstructed above, below or including the azygos vein. The object of the experiments was, primarily, to determine the tolerance of animals to occlusion of the superior vena cava, to measure the effects on venous pressures and to trace the paths of collateral circulation. Additional observations were made to determine the immediate effects of obstruction of the superior vena cava on the arterial blood pressure.

### EXPERIMENTAL METHOD

Dogs were anesthetized with ether, positive pressure with the intratracheal technic being employed. An intercostal incision was made aseptically on the right side of the chest, usually through the fourth intercostal space. The superior vena cava (the azygos vein in some instances) was approached transpleurally and exposed by blunt dissection. When the vessel had been cleansed for a distance of about 2 cm., it was doubly ligated at two points and divided between ligatures. The wound was closed by encircling interrupted heavy silk sutures about the two ribs adjacent to the wound. The lungs were inflated as these sutures were tied. The overlying muscles and the skin were then closed in layers.

*Obstruction Above the Junction with the Azygos Vein.*—This was accomplished in the manner just described in seven dogs.

*Obstruction Below the Junction with the Azygos Vein.*—In two dogs an attempt was made to occlude the superior vena cava below the point of junction with the azygos vein. As both of these dogs died within a few minutes, no further attempts were made to produce obstructions at this point.

*Obstruction Including the Azygos Vein.*—A two stage obstruction of the superior vena cava and the azygos vein was successfully accomplished in two of three experiments. In the first of these the azygos vein was obstructed in a preliminary operation. Seven weeks later a second stage operation was performed, at which time the superior vena cava itself was obstructed. This dog died within one hour. In the two dogs surviving the immediate effects of total obstruction of the superior vena cava produced in two stages, the superior vena cava was first

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1 Ehrlich, William; Ballon, H. C., and Graham, E. A.: Superior Vena Caval Obstruction, with Consideration of Possible Relief of Symptoms by Mediastinal Decompression. *J. Thoracic Surg.* 3:352 (April) 1934.

obstructed above the level of the azygos vein. The second stage procedure, consisting of the obstruction of the azygos vein, was performed twenty-three weeks later in one dog and twenty-eight weeks later in the other.

#### EXPERIMENTAL RESULTS

*General Observations.*—Immediately after the superior vena cava was obstructed above the azygos vein, the dogs showed marked cyanosis of the tongue and the oral mucosa and injection of the conjunctivae. They recovered from the anesthetic slowly, and some of them were stuporous for many hours. The respirations were slow and deep.

Six of seven dogs with occlusion above the junction of the azygos vein recovered from the immediate effects rather rapidly, so that within twenty-four hours the cyanosis had practically disappeared. They continued to appear listless for several days, refusing food and losing weight. Dilated veins appeared over the thorax and the upper part of the abdomen, and hematomas usually formed in the thoracic wounds. Within a week or ten days the dogs' appetites improved, and eventually three of the seven became active, well nourished, normal appearing dogs.

Two of the dogs died of empyema (within thirteen or fourteen days), and one of a wound infection and extensive thrombophlebitis (on the twelfth day). The only dog that failed to survive the immediate effects of the obstruction lived only two days, and there were no postmortem observations to explain its death.

Of the three dogs that regained their health, one was killed for further study after thirty days, and the other two were subsequently subjected to obstruction of the azygos vein.

In the two dogs in which obstruction below the point of junction of the azygos vein had been performed, a slow, deep respiration, followed by gasping breathing, developed. The upper part of the body was deeply cyanotic. Death was apparently due to respiratory failure.

The dog that had been subjected to obstruction of the superior vena cava after a preliminary obstruction of the azygos vein also died with deep cyanosis and failure of respiration. Cyanosis did not develop following obstruction of the azygos vein, even in the animals previously subjected to occlusion of the superior vena cava.

A serosanguineous pleural effusion developed in the first dog which survived the immediate effects of a total occlusion produced in two stages. The fluid was aspirated on three occasions, from 190 to 500 cc. being removed. The dog eventually died of bilateral empyema twenty-one days after the second stage procedure. The second dog, in which total obstruction was eventually performed, became well and active. He was finally killed for study at the end of thirty-six days.

*Development of Pleural Effusions.*—Except in two dogs that died of empyema, pleural effusions did not develop in the dogs in which

obstruction above the azygos vein had been carried out. In the only dog that was subjected to preliminary obstruction of the azygos vein a sanguineous effusion developed, from which he recovered within two weeks. At the time of the second operation for obstruction of the superior vena cava itself (seven weeks after the obstruction of the azygos vein) the fluid had been completely absorbed.

Bilateral pleural effusions developed in the two dogs with obstruction of the azygos vein and of the superior vena cava. In the case of the first dog the effusion became infected, and the dog died of bilateral empyema. The second dog regained good health, but when he was killed at the end of thirty-six days, postmortem examination revealed the presence of 200 cc. of clear brownish fluid in the right pleural cavity and 100 cc. in the left. The pleural fluid cannot be said to be due entirely to the venous obstruction, because the trauma incident to the opening of the pleura and the formation of a raw surface at the site of the ligation of the vein undoubtedly contributed. However, it is clear that pleural fluid is not absorbed as readily when both the superior vena cava and azygos vein are obstructed as when the azygos vein alone is obstructed or when the site of the occlusion of the superior vena cava is above the level of the azygos vein.

*Effect on Venous Pressures.*—Venous pressure readings were obtained by inserting a needle into the external jugular vein and measuring the height of the column of blood in an attached vertical 4 mm. glass tube. The vein was first exposed by cutaneous incision and blunt dissection. The pressure before operation varied between 4 and 13 cm. of blood. The high pressures sometimes noted were probably caused by the struggling of the animals, although they were under ether anesthesia when the pressure readings were taken. Venous pressure readings taken on four dogs immediately after obstruction of the superior vena cava (above the azygos vein) were found to average 100 per cent higher than the preoperative readings. Three readings taken during the first nine days were found to be 65 per cent higher than the original readings, but three readings taken from fourteen to twenty-nine days after the operation showed no significant average increase above the preoperative venous pressures.

The venous pressure after obstruction of the superior vena cava and the azygos vein was obtained for two dogs. The original reading in the first animal was 6 cm. The pressure immediately after the first stage procedure was 18 cm.; fifteen days later, 11 cm., and seven days after the second stage procedure, 16 cm. (an increase of 167 per cent). No preliminary reading was taken on the second dog. However, thirty-six days after the second stage operation (obstruction of the azygos vein) the pressure in the femoral vein (5 cm.) was compared with that in the



jugular vein (10 cm.). The pressure in the obstructed venous circulation was therefore 100 per cent higher than that in the nonobstructed vein, but even this pressure was within the limits of normal observed in some of the other animals.

The findings suggest that in obstruction above the azygos vein the venous pressure is definitely increased, but that as a result of collateral circulation it may eventually become normal. In the case of total obstruction the venous blood pressure was definitely elevated for at least thirty-six days, but the collateral circulation was sufficiently competent to permit the return to a level which does not exceed the upper range of venous pressures for normal dogs.

#### PATHS OF COLLATERAL CIRCULATION

The paths of collateral circulation represent one continuous anastomosing system which, however, may be arbitrarily divided into several different groups. A distinction between superficial and deep collateral veins is of importance because the superficial collateral veins are of greater clinical interest.

#### OBSTRUCTION ABOVE THE AZYGOS VEIN

*Superficial Veins.*—Tributaries of the axillary vein, chiefly the thoraco-epigastric vein, join a plexus of superficial veins over the thorax and abdomen. Superficial veins of the neck anastomose with those of the thorax, but these collateral veins are not prominent in the dog. The return flow of blood from the superficial veins occurs largely through the intercostal veins. Communications with the superficial epigastric and superior and inferior epigastric veins permit a return of blood through the femoral and external iliac veins, but the path through the external iliac veins is not well developed when the obstruction is above the level of the azygos vein.

*Deep Veins.*—(a) The internal mammary vein, a tributary of the innominate vein, is an important vessel in the collateral circulation (fig. 1). Anastomoses with the intercostal, anterior mediastinal and superior epigastric veins permit the return flow of blood to the heart.

(b) The veins of the mediastinum form a prominent plexus composed of the anterior mediastinal veins, a group of posterior mediastinal veins and the pericardiac veins. Below they enter the superior phrenic veins, tributaries of the inferior vena cava.

(c) A group of veins along the vertebral column, especially the internal vertebral plexus, communicate, above, chiefly with the dural sinuses and the vertebral veins and, below, with the intervertebral and intercostal veins.

(d) There is a plexus of deep veins of the back formed chiefly by posterior rami of the intercostal veins. Descending branches of the transverse cervical and transverse scapular veins also appear to enter into the formation of this deep dorsal group.

(e) The lumbar, abdominal and suprarenal veins communicating with the superficial and deep veins of the back and with the abdominal wall empty into the inferior vena cava. The lumbar veins also join the azygos system through the ascending lumbar veins.

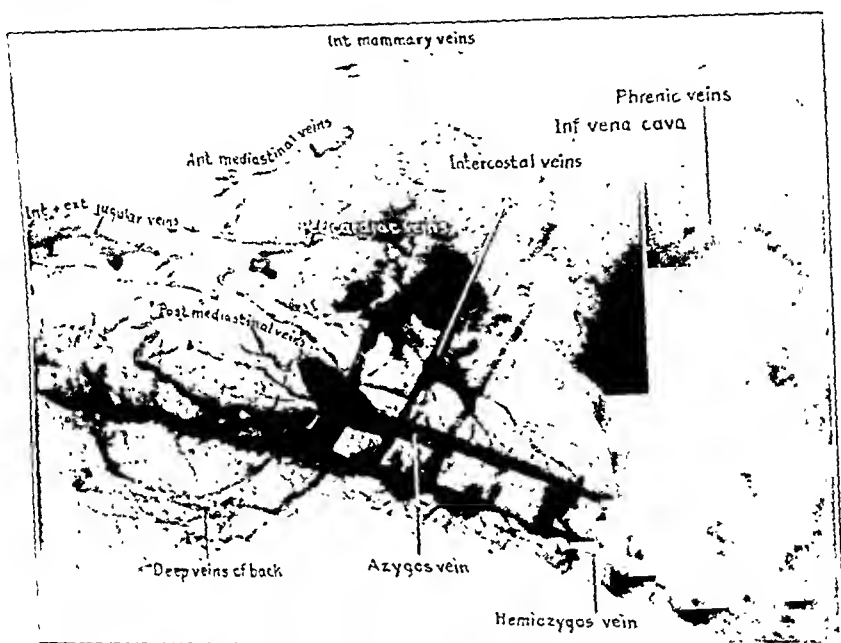


Fig. 1.—Injection of barium into the venous system to show collateral circulation after obstruction of the superior vena cava above the level of the azygos vein.

(f) The superior intercostal veins, other intercostal veins, and the accessory hemiazygos, hemiazygos and azygos veins form an important channel of collateral circulation.

In this type of obstruction (the superior vena cava being obstructed above the level of the azygos vein) the azygos vein with its tributaries becomes markedly distended and is the principal venous trunk through which blood returns to the heart from the upper part of the body.

#### COLLATERAL CIRCULATION AFTER OBSTRUCTION OF THE SUPERIOR VENA CAVA, INCLUDING THE AZYGOS VEIN

*Superficial Veins.*—The superficial veins are prominent over the chest and abdomen, beginning in the axilla chiefly with the thoraco-epigastric veins and terminating below in the superficial epigastric tribu-

teries of the femoral veins. The superficial veins anastomose freely with the deeper veins (fig. 2).

*Deep Veins.*—(a) The internal mammary and the superior and inferior epigastric veins form a path from the innominate vein above to the external iliac vein below (fig. 3).

(b) The pericardiac veins and the anterior and posterior mediastinal veins form a well developed plexus of collateral veins traversing the mediastinal space.

(c) The vertebral venous plexuses are extensively developed, particularly the internal vertebral plexus, which may be traced clearly

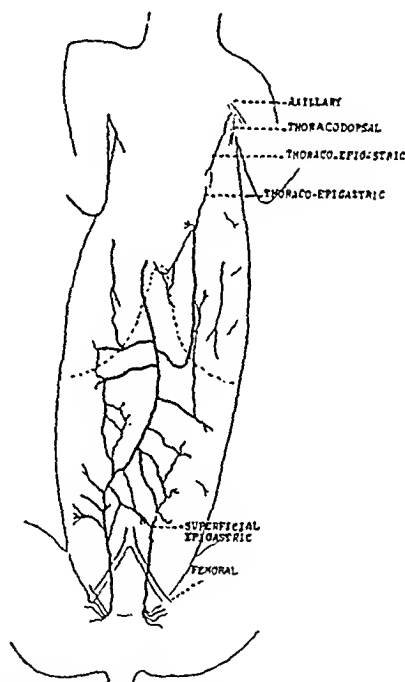


Fig. 2 (dog A-15).—A dissection of the superficial venous system after obstruction of the superior vena cava, including the azygos vein.

from the cervical to the lumbar region. The intervertebral, intercostal and lumbar veins anastomose with these plexuses.

(d) The deep collateral veins of the back are present, but are not prominent. They may be traced down to the lumbar region.

(e) The suprarenal, lumbar and abdominal veins of the dog communicate with the deep and superficial veins of the lumbar region and enter the inferior vena cava.

(f) The azygos system, being obstructed, is diminished in size, and the flow of blood through it is apparently reversed.

The differences between the paths of collateral circulation in the two types of obstruction may be summarized briefly. In the first type the azygos vein and its tributaries form the chief venous trunk for the

return flow of blood from the upper part of the body to the heart. The lower abdominal collateral veins are relatively unimportant. In the second type of obstruction the superficial and deep abdominal vessels and the vertebral plexuses are of much greater importance. As the azygos vein is blocked, all of the blood returns to the heart through the inferior vena cava.

In experimental studies of human cadavers, Wagner<sup>2</sup> found that the renal and the internal spermatic veins were important paths of collateral circulation, but they did not appear to be well developed in the experiments on dogs reported here.

Wagner also found that the superficial dorsal thoracic veins were more prominent when the obstruction was below than when it was

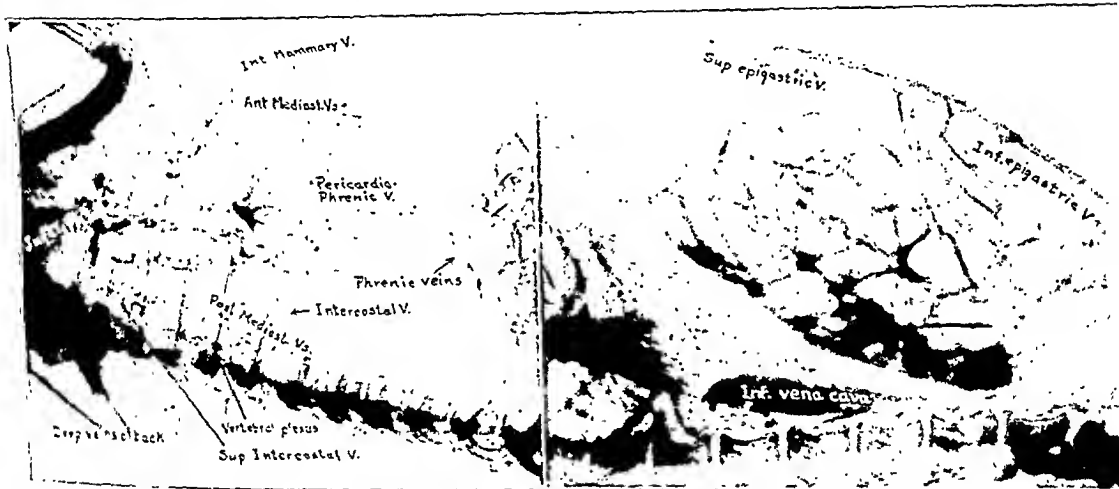


Fig. 3.—Injection of barium into the venous system to show collateral circulation after obstruction of the superior vena cava, including the azygos vein. The portal vein was apparently filled by back pressure. It did not prove to be a path of collateral circulation.

above the point of junction with the azygos vein. Dorsal superficial collateral veins were not well developed in the dog in either type of obstruction. No striking differences could be observed in the two types studied.

#### THE EFFECT ON ARTERIAL BLOOD PRESSURES

Carotid blood pressure tracings were taken on three dogs, the superior vena cava and the azygos vein being obstructed simultaneously through an open pneumothorax. In these experiments respiration was maintained by means of rhythmically interrupted positive pressure.

2. Wagner, K.: Symptomatology of Stenosis with Occlusion of Lumen of Superior Vena Cava. *Polska gaz. lek.* 11:61 and 81, 1932; abstr., *J. A. M. A.* 95:1342 (April 9) 1932.

Three experiments of this type showed that sudden total obstruction of the superior vena cava results in a drop of the arterial blood pressure to shock levels (fig. 4). Following the release of the obstruction a plethoric effect was noted, the blood pressure rising to a level higher than that preceding the obstruction, after which the blood pressure eventually became level again. The effect of prolonged obstruction was also noted (fig. 4). A sudden drop in arterial pressure occurred immediately after the superior vena cava was obstructed. From that time on there was a progressive drop in the pressure which, however, occurred slowly. The respirations became slow; after thirty minutes they were succeeded by gasping efforts. Finally all of the respiratory movements ceased, and respiration was entirely artificial. The heart action continued more than thirty minutes after the cessation of respiratory movements.

#### Carotid Blood Pressure

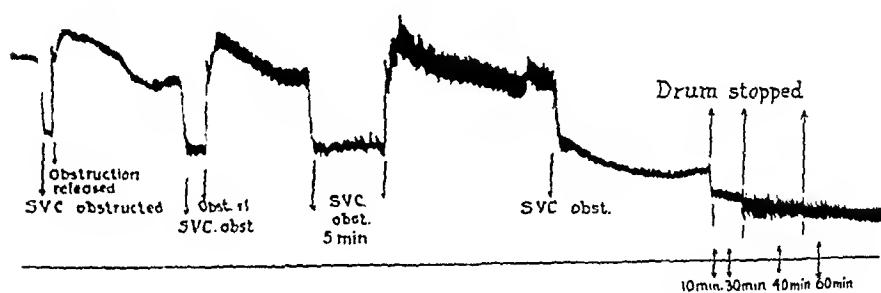


Fig. 4.—The effect of sudden, complete obstruction of the superior vena cava and azygos vein on the arterial blood pressure.

These changes in arterial blood pressure are probably not of much clinical significance, because the occlusion of the vessel usually occurs slowly in clinical cases. However, the rapid death of animals subjected to sudden total obstruction of the superior vena cava is apparently a result of the disturbed circulation of the respiratory center and other vital centers. This disturbed circulation consists of a fall in arterial blood pressure and a rise in venous pressure due to venous stasis. Changes in the oxygen and carbon dioxide tension of the blood were not investigated.

#### SUMMARY

Obstruction of the superior vena cava was produced above and below the azygos vein in such a way as to include the azygos vein. Dogs tolerate obstruction above the level of the azygos vein but not obstruction below the azygos vein when it is produced in one stage. Obstruction of the superior vena cava and the azygos vein may be produced successfully in two stages.

Marked cyanosis of the upper part of the body results from obstruction of the superior vena cava, but as collateral circulation develops, the cyanosis disappears. The collateral circulation eventually compensates for the obstruction, so that the animals appear healthy, and the venous pressures of the obstructed area become normal or are only slightly elevated. The paths of collateral circulation have been described.

The arterial blood pressure immediately after obstruction of the superior vena cava (including the azygos vein) drops to a shock level.

# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Stone.*—Gayet<sup>1</sup> pointed out the difficulty encountered when lithiasis occurs in a solitary, infected kidney or bilaterally in kidneys with the renal parenchyma in an advanced stage of destruction. He reported 2 cases of this type in which minor operative procedures, such as incision of the renal parenchyma with insertion of an individual indwelling catheter and the opening of a perinephric abscess, had kept the patients from succumbing to the disease and had relieved them at least temporarily. In 1 case the right kidney was practically functionless whereas the left kidney contained a large stone. In the other case, the stone was in a horseshoe kidney; the urine was purulent, and there was a perinephric abscess communicating with the pelvis.

Most of the patients with these conditions are uremic and cannot endure a long operation under general anesthesia. The period of operation must be brief, and as a rule exteriorization of the kidney must be avoided as the organ may be acutely infected and may at times lie in the midst of a perinephric abscess. Fever and tension should first be reduced by nephrostomy; later, the calculi should be removed, so far as possible, through the opening made at nephrostomy by means of a finger, a blunt curet or fenestrated forceps. Only minor operative procedures may be performed in cases in which the kidneys are badly infected. Treatment should consist of such minor operative procedures repeated

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1. Gayet, G.: Néphrolithotomies en plusieurs temps dans les cas graves de lithiase rénale, Bull. Soc. franç. d'urol., Jan. 15, 1934, p. 35.

as necessary; these procedures should be meticulously prepared for and followed by close surveillance afterward.

Nash<sup>2</sup> studied calculous pyonephrosis with a view toward clearing up some of the problems presented by this disease, especially toward bringing out the value of transperitoneal nephrectomy, devised recently to obviate the difficulties involved in secondary lumbar nephrectomy which is always required sooner or later after nephrotomy has been performed as a palliative measure. If a surgeon makes the mistake of performing a nephrectomy in one stage when the patient is run down, he is likely to lose that patient. Even in operations performed in two stages by the lumbar route there is still the danger of operating on a patient who is in poor condition and who has a kidney densely adherent to surrounding structures, nephrotomy not only having failed to eliminate the old adhesions but having also complicated the picture by removing the normal landmarks and creating new ones of scar tissue. Bleeding also complicates the situation and brings additional dangers.

Transperitoneal nephrectomy obviates these difficulties because the approach is through a fresh field. The abdomen is opened by a pararectal incision. The ureter, which is readily identified, is easily followed up to the pedicle, and the renal vessels can be ligated before any attempt is made to enucleate the kidney proper. Any adhesions present may be separated under vision without the disturbing element of uncontrollable bleeding.

In most cases of calculous pyonephrosis the patients are young women who have married at an early age and have gone through many and frequent pregnancies. It is suggested that urinary diathesis may predispose these women to an infection and to the formation of stone in the kidneys analogous to those in women with biliary diathesis in whom disease of the gallbladder originates at the time of their first pregnancy.

[COMPILERS' NOTE.—Although transperitoneal nephrectomy is best indicated for renal neoplasms, it should not be used systematically instead of typical lumbar nephrectomy because in most instances of calculous pyonephrosis in which the kidney has become greatly enlarged besides the shock of the operation there is the possibility that peritonitis may develop, and this, of course should always be avoided.

Gutierrez has stressed the value of lumbar nephrectomy in two stages, following preliminary drainage by nephrostomy, for highly debilitated patients for whom a hasty one-stage nephrectomy may have fatal results. It has been shown that these patients improve when the shock of the operation is thus divided, since they are able to build up

2. Nash, J. E.: Calculous Pyonephrosis: A Clinical Study with Special Reference to Etiology and Treatment; Review of the Literature, Report of Six Cases. *Am. J. Surg.* 24:110 (April) 1934.



bodily resistance and to gain in renal function, resulting in cardiac compensation and in general detoxication. By this two step procedure a greater measure of safety is assured both to the patient and to the surgeon, and it is likewise obvious that it has served to reduce the mortality appreciably, particularly in cases of pyonephrosis in which the kidney has become considerably enlarged and in which nephrectomy by the lumbar route carried out extraperitoneally is correctly indicated.]

Quinby<sup>3</sup> stated that in the five years preceding 1931, 240 patients with renal or ureteral calculus were admitted to the Peter Bent Brigham Hospital. This period marks the beginning of his endeavor to adopt a consistent policy toward urinary stone, which was as follows: (1) to conserve renal tissue whenever possible by employing nephrectomy only when renal injury was great; (2) to consider the operation that removes a stone only the first event in the medical care of the patient, and to insist that whenever possible each patient return at suitable intervals for antiseptic treatment of the bladder and kidneys; (3) in cases in which operation is needed to persist until the roentgenogram taken at the operating table reveals that all the stones have been removed.

Of the 240 patients, 76 hospital patients and 45 private patients were available for the present analysis. A roentgenogram was taken of all the hospital patients when they returned; they received a general physical examination, and the urine was analyzed and cultured. Letters from the private patients or from their physicians were at times accepted instead of personal interviews.

One hundred and twenty-one patients were considered. One patient died at operation. Three other patients were not relieved and died later, giving a total mortality rate of 3.3 per cent. In 64 cases the stone or stones were situated in the kidney, and in 3 cases the stones were in both the ureter and the kidney. There were 6 cases of bilateral stones and 2 cases of unilateral stone. On the follow-up records of patients with renal stone, Quinby found that the stones had recurred in 21 cases (in 5 of the cases in which the stone was bilateral all the stones had not been removed at operation). Therefore, in 24, or 19.8 per cent of 121 cases, stones were still present. Further analysis has revealed that in nearly all the cases failure to relieve these patients permanently has been due to persistence of the original infection. It is clear, therefore, that, after a certain degree of renal injury has taken place, one is well-nigh powerless to conquer the coincident infection, even though persistent effort is made after the stone has been removed. Nephrectomy was performed in 24 cases as compared with 45 cases in which the calculus was removed by pyelotomy or by pyelonephrectomy. Although

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3. Quinby, W. C.: *End-Results of Operations for Lithiasis*, Tr. Am. A. Genito-Urin. Surgeons 26:285, 1933.

the majority of the patients who underwent nephrectomy were cured, the subsequent formation of multiple stones in the remaining kidney of 3 patients led to further operation and eventually to the death of 2.

Quinby stated that from all this study it appears that ureteral stones are likely to be associated with less infection and less injury to the kidney than stones which do not enter the ureter. This is doubtless largely due to the fact that urgent symptoms are caused by these relatively small stones at a much earlier date. Patients with renal calculi should be subjected to operation for the removal of such stones at an early date. It is a mistake to delay operation because the stone is causing no symptoms. The problem of urinary infection plays a large part in the incidence of formation of stone, and the end-result of the treatment of the stone depends considerably on the degree of such infection and on the physician's ability or inability to conquer it.

*Tumor.*—Simpson<sup>4</sup> considered the diagnosis, pathologic changes and treatment of carcinoma of the kidney. In his experience carcinoma of the kidney, in contradistinction to hypernephroma, papillary carcinoma of the renal pelvis and the embryonal adenocarcinoma of children, gives rise to a syndrome characterized by: (1) severe pain in the back, which is constant, is unaffected by exercise and is caused by extension of the growth to the upper lumbar vertebrae; (2) hematuria, usually of short duration without recurrence, and (3) absence of any obvious enlargement of either kidney. Objective findings of unilateral reduction of function and collapse of one or more lumbar vertebrae complete the diagnosis. Following retrograde pyelography, the absence of pelvic deformity in early cases may be misleading. Even in advanced cases there may be little pelvic abnormality. Simpson considered involvement of the upper lumbar vertebrae to be the result of local extension through lymphatic structures rather than of metastasis, and in support of this contention he quoted the report of a case of Fraser's in which only half of the body of the first lumbar vertebrae was involved on the side of the affected kidney.

In contrast to other renal tumors carcinoma infiltrates and replaces renal tissue without perceptible enlargement, so that clinically there is no palpable tumor.

Four cases are reported, in all of which these characteristic symptoms were present.

Kimball and Ferris<sup>5</sup> stated that the pelvis of the kidney is involved by neoplasms much less commonly than the renal parenchyma. In 1924,

<sup>4</sup> Simpson, Graham: Carcinoma of the Kidney, *Brit. J. Surg.* **21**:388 (Jan.) 1934.

<sup>5</sup> Kimball, F. N., and Ferris, H. W.: Papillomatous Tumor of the Renal Pelvis Associated with Similar Tumors of the Ureter and Bladder; Review of Literature and Report of Two Cases, *J. Urol.* **31**:257 (March) 1934.

Thomas and Regnier reviewed 248 cases in which tumors invaded the renal pelvis, ureter and bladder; they found that the renal pelvis alone was involved in 33 per cent, the renal pelvis and ureter in 14 per cent, and the renal pelvis, ureter and bladder in 8 per cent of the cases. Papillary tumors of the renal pelvis grow slowly and cause profuse hematuria. This hematuria, often massive and sometimes painless, is the most predominant symptom; it occurred in 96 per cent of 74 cases studied by Kimball and Ferris. It occurs comparatively early in the course of this condition. The longest duration recorded was of intermittent hematuria over a period of twenty years. Pain was usually caused by secondary obstruction resulting from intermittent and variable hydronephrosis. It was accompanied by hematuria in 52 per cent of the cases. In only 15 per cent could a mass be felt and, when a mass was palpable, it was usually cystic and soft, and was caused by hydronephrosis.

Kimball and Ferris stated that cystoscopic data are extremely significant in cases of tumor of the renal pelvis. It was the means of diagnosis in 85 per cent of the cases studied. The growth usually originates in the wall of the renal pelvis and occasionally invades the parenchyma. The tumor may vary from a small, localized tuft to an extensive mass that completely fills and distends the pelvis. The metastatic growths in the bladder may be either single or multiple, and they usually are near the affected ureteral orifice. The ureteral orifices and adjacent bladder were involved in 48 per cent of the cases of Kimball and Ferris. At the time the reports of the cases were published there were known recurrences in 64 per cent of the cases and no known recurrences in 32 per cent after removal of the primary tumor. The original tumor was malignant in 38 cases, or 51 per cent, and benign in 36 cases, or 49 per cent. In the group in which the original tumor was malignant the recurrences were malignant in 75 per cent and benign in 20 per cent of the cases.

Kimball and Ferris stated that tumors of the renal pelvis are inherently malignant and that the microscopic characteristics of benignancy do not insure innocent behavior on the part of the tumor. Recurrences in the lower segments of the ureter and in the bladder have often been observed. In Kimball and Ferris' series of 74 collected cases, 40 patients were treated by nephrectomy and 25 by nephro-ureterectomy, including the intramural part of the ureter. Thirty, or 75 per cent of the 40 patients who underwent nephrectomy, are known to have had recurrences. Secondary ureterectomy was performed on 21 of these patients, with further recurrences in 12, or 57 per cent. The known mortality in the group treated by nephrectomy was 33 per cent. Primary nephro-ureterectomy, without including the intramural part of the ureter, was performed in 25 cases. There were known recurrences in 17, or

68 per cent, of these cases. Further resection of the intramural part of the ureter was done in 12 cases, with still further recurrences in 4 cases. The known mortality for this group was 44 per cent. In only 6 cases was primary nephro-ureterectomy, which included the intramural part of the ureter, performed. In 2 of these cases the diagnosis was benign tumor and in 4, malignant tumor. The known mortality in the group of cases of malignant tumor was 25 per cent. Of the total of 74 patients, 28 were known to have died, a mortality of 38 per cent.

Kimball and Ferris state their belief that in the treatment of papillomatous tumors of the renal pelvis, nothing short of primary, complete nephro-ureterectomy, with resection of the intramural part of the ureter should be considered.

*Hydronephrosis.*—Fagge<sup>6</sup> presented a case of advanced hydronephrosis of the right kidney, in which the symptoms were referable chiefly to the gastro-intestinal tract. For years the patient had had indigestion, with attacks of pain, nausea and vomiting, suggestive of an intermittent duodenal obstruction. These attacks had been brought on and relieved by a change of posture.

A study of the gastro-intestinal tract revealed compression, marked elongation and mesial displacement of the second portion of the duodenum. There was no palpable mass, but an excretory urogram revealed advanced hydronephrosis of the right kidney with a large extrarenal pelvis displacing the duodenum. Removal of the kidney completely relieved the gastro-intestinal symptoms.

[COMPILERS' NOTE.—Silent hydronephrosis is not uncommon. There may be advanced hydronephrotic atrophy without any symptoms referable to the urinary tract. This is especially true of hydronephrosis of the left kidney. When the right kidney is involved, however, and especially when there is large extrarenal pelvic dilatation because of its relation to the second portion of the duodenum, the symptoms may be predominantly or entirely gastro-intestinal, with a syndrome characteristic of gastroduodenomesenteric ileus or intermittent duodenal obstruction.

During an attack relief may be obtained by changes in posture; the extreme Trendelenburg position usually gives relief.]

Hinman,<sup>7</sup> in an experimental study of hydronephrosis, has thrown light not only on the mechanism of this condition but also on the causes of many other renal disturbances. Complete obstruction of the excretory ducts of other glands (salivary, pancreatic and biliary) produces primary

<sup>6</sup> Fagge, C. H.: Case of Hydronephrosis. *Brit. J. Surg.* **21**:151 (July) 1933.

<sup>7</sup> Hinman, Frank: Pathogenesis of Hydronephrosis. *Surg., Gynec. & Obst.* **57**:356 (Feb.) 1934.

atrophy and necrosis, but complete obstruction of the ureter results in a condition that is unique, namely, progressive hydronephrotic atrophy. Primary atrophy occasionally occurs, and the secondary changes vary, giving the picture of a secondarily contracted kidney, of the changes caused by infection or of attempts at repair.

The results of the experimental work of Hinman are summarized under five headings: (1) pathologic changes produced by ureteral obstruction; (2) effect of prolonged modification of secretory pressure on the rate of the production of these changes; (3) effect of relief of obstruction on these changes; (4) relation of structure to these changes, exemplified by the comparative variations in living forms, and (5) relation of renal hydromechanics to the production of hydronephrosis and primary atrophy.

1. The pathologic changes produced by complete ureteral obstruction in the unipapillary kidneys of the rabbit or dog are characterized by progressive pelvic distention and by parenchymal atrophy. The pathologic changes of hydronephrosis in the metanephros of the rabbit are characterized by progressive ureteropelvic distention and by parenchymal atrophy. The tubules undergo dilatation, collapse and atrophy. The glomeruli persist longest. The changes are found in groups of structures and are not diffuse and uniform. This early atrophy of certain groups and the relative preservation of others are related to the blood supply. Both pelvic and tubular distention affect the renal circulation. Back pressure is the primary and essential factor, but anemic atrophy is the more active and controlling factor in producing the changes of hydronephrotic atrophy.

2. The effect of prolonged modification of secretory pressure (intrapelvic pressure) on the rate of development of hydronephrosis was studied by producing polyuria and oliguria, by lowering secretory pressure through prolonged partial constriction of the renal artery and by raising secretory pressure through prolonged partial constriction of the renal vein. It might be assumed that variations in intrapelvic back pressure would cause proportionate variations in the rate of development of hydronephrotic atrophy. It was found, however, that experimentally this was not so, and that polyuria or oliguria in no way modified the rate of progressive dilatation. The slightest modification of the blood supply producing parenchymal anemia hastened the dilatation to a marked degree, even when the intrapelvic pressure was lowered at the same time; this indicated that although increased intrapelvic pressure is essential to hydronephrotic atrophy, the rate of development is largely determined by the secondary circulatory changes with the resultant anemic atrophy.

3. The effect of the removal of the ureteral obstruction on hydronephrotic atrophy was studied by ligating and dividing one ureter near

the bladder, so that later the obstruction could be relieved and the ureter transplanted into the bladder. Modifications of the rate of repair were studied by varying the stimulus or demand for repair by operations on the opposite normal kidney, that is, by nephrectomy at varying periods or by slow destruction of the kidney through partial obstruction of its ureter. It was found that the repair of hydronephrotic atrophy, following removal of the obstruction of the ureter, is characterized grossly by shrinkage in size and microscopically by the return of the less injured groups of glomerulotubular units to a more normal appearance. The glomerular and convoluted portions of the units in which repair has taken place show hypertrophic changes. Restoration of function is proportional not only to the number of structural units in which repair takes place but also to the degree of hypertrophy in each. With repair the same stage of hydronephrotic destruction shows, in different kidneys, a variation in the degree of these hypertrophic changes according to the nature of the excretory burden placed on the kidney at the time the obstruction in the ureter is removed. The maximal amount of repair of structure and restoration of function follows a gradual shifting of the burden, such as follows slow destruction of the opposite kidney.

4. The question arises whether hydronephrotic atrophy is peculiar to or dependent on the structural arrangements as seen in mammals in which the kidneys are metanephric, either unipapillary without columns of Bertin or multipapillary with such columns. The arrangement of the pelvis to the blood supply is intimate. All other kidneys are without a pelvis, and the blood vessels enter on the side opposite the excretory duct. The question arises: Can hydronephrosis develop with this structural arrangement? It was found that the pathologic changes of hydronephrosis occur only in kidneys which have internal glomeruli. The gross and microscopic changes occur most typically in the mammalian kidney, which has a hilus and a pelvis. This structural arrangement, however, is not essential. Similar changes follow complete obstruction of the ureter or of the primary excretory duct of the apeliac kidneys of reptiles, birds and amphibians. The microscopic changes which follow the direct obstruction of tubules in the pelvic type of kidney, such as occurs when a papilla has been tied, resemble those which follow indirect obstruction, such as occurs when the ureter has been tied.

5. The development of hydronephrosis presupposes the continuation of renal activity with the maintenance of intrapelvic pressure. This can take place only if there is resorption. There has to be an inflow and outflow, and this can take place only through resorption when the ureter is completely blocked. This theoretical assumption is confirmed by experimental observations. The mechanical factor in the development of hydronephrotic atrophy is a backflow of urine into the venous

system. In mammalian kidneys this backflow is probably at first pyelovenous and later becomes tubulovenous. In the apelvic mesometanephros of the reptile, bird and amphibian the backflow fails to occur on complete obstruction of the excretory duct; anuria develops, and the pathologic change of primary atrophy, instead of hydronephrotic atrophy, results.

Mathé and de la Peña<sup>8</sup> stated that a high percentage of failures has been reported by surgeons who, having previously performed plastic operations on the kidney for hydronephrosis, have checked their results after operation by the ureteral catheter, by studies of renal function and by pyelography. These failures are due to the following factors: improper or insufficient correction of the obstructing lesion in the upper part of the ureter and ureteropelvic juncture, improper selection of the particular type of plastic repair for each individual case and lack of appreciation of certain technical points that are necessary for permanent relief of renal retention and hydronephrosis. The most common causes of failure in correcting etiologic obstructive lesions are: buckling of the mucosa following the Fenger operation of longitudinal incision and transverse closure for stricture and valve formation of the ureteropelvic juncture, lack of proper disposition of obstructing, anomalous vessels, neglect to perform thorough ureterolysis and failure to employ nephropexy.

The most common causes of hydronephrosis in the upper part of the ureter are: (1) movable kidney, with angulation of the ureter over anomalous blood vessels, angulation over fibrous bands in the perirenal tissues and angulation due to the collapse and adhesion of the ureter against the side of the pelvis; (2) lateral insertion of the ureter; (3) inflammatory contracture or stricture of the ureteropelvic juncture; (4) formation of calculi in the upper part of the ureter and pelvis, and (5) sclerosing, infectious and traumatic perinephritis. Patients with early hydronephrosis secondary to a movable kidney associated with angulation of the ureter, in whom the angulation is due to fibrous bands or to a collapse of the ureter and adhesion to the pelvic wall, can usually be relieved by ureterolysis and by nephropexy. Hydronephrosis secondary to smaller aberrant vessels is best relieved by ureterolysis, resection of the vessels and nephropexy. In cases of early hydronephrosis caused by a stricture of the ureter of large caliber and formation of valves at the ureteropelvic juncture, relief can be obtained by longitudinal incision with transverse closure. In advanced cases of formation of a stricture, resection of the sclerotic ureteropelvic juncture, reimplantation of the ureter into the pelvis and temporary nephrostomy

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8. Mathé, C. P., and de la Peña, Emilio: *Surgical Repair of Hydronephrosis, with Reference to Technical Points Favoring Relief*, J. Urol. **31**:1 (Jan.) 1934.

are indicated. In hydronephrosis due to sclerosing, infectious and traumatic perinephritis, nephrolysis and ureterolysis should be performed, and the type of repair which is based on the nature and extent of the hydronephrotic sac should be utilized.

*Single Kidney in Pregnancy.*—Prather and Crabtree<sup>9</sup> stated that, in general, nephrectomy is not a contraindication to pregnancy. They reported the cases of 296 women who had undergone nephrectomy, 365 pregnancies having subsequently developed among these women. In 55 per cent of these cases nephrectomy had been performed because of tuberculosis. Renal pelves and the upper part of the ureters undergo the familiar type of dilatation encountered during pregnancy. The right kidney reveals a greater degree of dilatation than the left kidney. If the kidney is normal tests of renal function reveal an adequate margin of safety during pregnancy. The study of these patients should include thorough physical examination, repeated examinations of catheterized specimens of urine, inoculation of guinea-pigs with specimens of urine from patients who give a history of tuberculosis of the urinary tract, studies of the blood, two hour tests with phenolsulphonphthalein and intravenous pyelography.

Many early investigators advised against marriage for the woman who had undergone nephrectomy. Accumulated statistics indicate a mortality rate of from only 1.09 to 1.4 per cent. In patients who on examination are not found to have any abnormalities pregnancy should always be allowed to continue, though under close observation. Prather and Crabtree believed that the desire to avoid permanent renal injury, combined with closer study, may in the future result in a somewhat higher percentage of interruptions of pregnancy; the indications for such interruptions are: the finding of an injured kidney early in pregnancy and obstetric or renal complications later.

*Supernumerary Kidney.*—Saccone and Hendler<sup>10</sup> reported the accidental finding of a supernumerary kidney at necropsy. There was no communication between the two kidneys, which were on the left side; each had a separate supply of blood and a separate ureter, the ureters fusing below the pelvic brim and outside of the bladder. In this case the supernumerary kidney had been a normal, functioning, independent organ, as was revealed by its anatomic position and by microscopic study. Symptoms referable to the genito-urinary tract had never been noted. The total number of such cases reported, including this one, is 36.

9. Prather, G. C., and Crabtree, E. G.: The Lone Kidney in Pregnancy, *Tr. Am. A. Genito-Urin. Surgeons* 26:313, 1933.

10. Saccone, Andrea, and Hendler, H. B.: Supernumerary Kidney: Report of a Case and Review of the Literature, *J. Urol.* 31:711 (May) 1934.



*Hemipyonephrectomy.*—Campbell<sup>11</sup> reported 5 cases of hemipyonephrosis among young children. Double kidneys are more prone to disease than normal organs. This lesion may cause persistent urinary infection among juveniles and, because of pyuria, the diagnosis of chronic pyelitis is commonly made. Complete urologic examination is essential to the correct diagnosis of hemipyonephrosis. Ureteroheminephrectomy is the treatment of choice when half of the double kidney remains undiseased, and the operation is technically feasible if the condition of the patient permits. If marked renal infection is present, especially if it is acute, nephrectomy is often the best procedure. Ureteroheminephrectomy was successfully performed in the case of an infant 6 months of age, the youngest patient in this series.

*Perinephric Abscess.*—Kessler, Bennetts and Bacon<sup>12</sup> stated that pathologic processes that present practically all the signs and symptoms of perinephric abscess may lie entirely outside the renal fossa. When surgical exploration for perinephric abscess is unsuccessful, there should be careful consideration and diagnostic investigation of all the structures adjacent to the kidney. In this region suppuration of structures other than the kidney and perinephric fat have the same etiologic background, that is, hematogenous infection from foci of suppuration elsewhere, and such conditions occur with sufficient frequency to warrant their consideration in cases of suspected perinephric abscess.

*Polycystic Disease.*—Walters and Braasch<sup>13</sup> stated that the contention that surgical treatment of polycystic kidney is seldom if ever indicated, is erroneous. Complications with polycystic kidney that require surgical treatment occur frequently. The estimation of renal function is of fundamental importance in determining the prognosis and advisability of operation. Owing to anatomic conditions present in the polycystic kidney, retention tests of renal function usually give a better index than excretory tests. Evidence of marked disturbance of function in both kidneys, such as is indicated by a value for urea of from 50 to 60 mg. or more per hundred cubic centimeters of blood, is usually a contraindication for surgical treatment except as an emergency measure. When complications indicating nephrectomy are present in one kidney it is essential to determine first whether the degree of function of the other kidney is sufficient to sustain life. Bilateral renal deformity, visualized by intravenous or by excretory urography,

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11. Campbell, M. F.: Hemipyonephrosis in Infants and Children, *Am. J. Surg.* **21**:85 (July) 1933.

12. Kessler, E. E.; Bennetts, F. A., and Bacon, S. K.: Perinephritic Abscess, *Am. J. Surg.* **22**:223 (Nov.) 1933.

13. Walters, Waltman, and Braasch, W. F.: Surgical Aspects of Polycystic Kidney, *Tr. Am. A. Genito-Urin. Surgeons* **26**:385, 1933.

should serve to make evident the comparative degree of function in either kidney and to govern the type of operation and its advisability. A polycystic kidney has not infrequently been removed after a clinical diagnosis of renal tumor.

The most common complication occurring with a polycystic kidney and requiring surgical treatment is diffuse or localized infection. Diffuse, subacute renal infection may have an insidious onset, and there may be but few localizing symptoms. Renal pain is a common symptom and is usually described as a dull ache, although it may become acute. It may be caused by excessive renal weight, exerting a pull on the renal pedicle, by intracystic or external pressure or by infection. Puncture or enucleation of one or more large cysts may serve to ameliorate the condition or to eradicate pain. Hematuria, usually of moderate degree and of limited duration, may become copious and long continued. Such hematuria is usually the result of intracystic hemorrhage, with rupture of the cyst into the renal pelvis. Excision or enucleation of such cysts usually suffices to control the hemorrhage. Should destruction of the kidney be extensive accompanied by secondary infection, nephrectomy may be necessary. Other complications observed with polycystic kidney are renal calculus, neoplasm, tuberculosis and hydronephrosis.

*Nephrostomy.*—Cabot<sup>14</sup> stated that, as a rule, reimplantation of the ureter into the bladder is not mechanically feasible. The results are by no means satisfactory, and pyonephrosis, at least, commonly results. This raises the question of implantation of these injured ureters into the bowel. Transplantation of a ureter made abnormal as the result of obstruction is, however, attended by a risk considerably greater than that attending the transplantation of a normal ureter. This increased operative risk has seriously interfered with surgeons' willingness to undertake the operation.

In the last two years Cabot has been interested in studying the possibility that preliminary nephrostomy, resulting in adequate drainage of the kidney, would eliminate the additional risk and make transplantation of these ureters a sound undertaking. His experience with 3 such cases, in 1 of which bilateral nephrostomy and bilateral ureteral transplantation were performed (3 patients and 4 ureters), is encouraging. Nephrostomy has had the effect of maintaining the function of the kidney and of apparently improving it; transplantation, carried out after an interval of several weeks, has proved simple and satisfactory. It has been notable that the technic of the operation has been easy; wounds have healed nicely, and there has been a notable absence of

<sup>14</sup> Cabot, Hugh: Nephrostomy Preliminary to Transplantation in Cases of Injury to the Ureter, Proc. Staff Meet., Mayo Clin. 9:125 (Feb. 28) 1934.

fever postoperatively. Drainage has been continued for about two weeks after transplantation, and then, on removal of the tube, the ureter has gone into action without incident and with prompt closure of the wound. In fact it has been surprising that the wounds made at nephrostomy have not leaked after the first twenty-four hours following removal of the tube.

Cabot presented in some detail a case in which bilateral nephrostomy had been performed; both ureters had been transplanted, at separate times. This case, coupled with the 2 in which the procedure was of shorter duration, suggests that under these conditions nephrostomy as a preliminary to ureteral transplantation can be performed with a low immediate mortality rate and with at least as good probability of maintaining the integrity of the kidney as by any other method. It also suggests that preliminary nephrostomy diminishes the risk of transplanting the ureter.

Gutierrez<sup>15</sup> has called attention to the desirability of performing carefully planned nephrectomy in two stages in cases of advanced pyonephrosis in which the patient is too ill to be subjected to primary nephrectomy, especially when a perinephric abscess is present or when tuberculosis or calculous pyonephrosis is accompanied by an enormous enlargement of the kidney and by grave, toxic symptoms. The same principle should be followed in renal as in general surgery. Drainage of a pyonephrotic kidney to relieve the gravity of the symptoms before a radical operation is undertaken is a logical procedure, and it may be the means of saving the life of the patient.

The most important indications for this combined procedure are observed in anuria caused by calculus, in infected hydronephrosis, in pyonephrosis with perinephric abscess, in hydro-ureteropyonephrosis with or without calculus, in tuberculous pyonephrosis, in certain types of nephrolithiasis and in surgical nephritis. It is also indicated after nephrolithotomy or after pyelotomy for the removal of calculi and for derivation of the urine when the ureter is incapacitated, as well as in certain types of congenital malformations, such as horseshoe kidney with bilateral hydronephrosis, pyonephrosis or nephrolithiasis. It has its widest application when its primary purpose is the relief of urinary symptoms arising from retention and infection. The most important point lies in minimizing the surgical shock produced by the removal of extensive pyonephrosis, thus enabling the patient to build up bodily resistance by a course of general detoxication, strengthening of the cardiac and renal function and relieving of septic symptoms, chills, fever, acute urinary disturbance and general autointoxication.

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15. Gutierrez, Robert: Nephrostomy as a Preliminary Drainage in Preparation for Secondary Nephrectomy, *J. Urol.* **31**:305 (March) 1934.

Secondary nephrectomy is not always easy to perform owing to the presence of long-standing adhesions, but with a correct preoperative diagnosis it can be performed without danger. It should be performed as soon as the patient's general condition permits. Nearly every secondary nephrectomy becomes a subcapsular procedure, owing to the difficulty of exposing the kidney and of controlling the bleeding in some cases. In subcapsular nephrectomy as much as possible of the fatty capsule should be removed to prevent suppuration and to aid in healing of the wound.

Livermore<sup>16</sup> stated that the benefit from nephrostomy does not seem to be appreciated by the profession. Although Cabot and Holland and Boyd and others have reported how satisfactorily it has served them, it is not being used as often as its worth demands. Because of his appreciation of the value of nephrostomy, Livermore has presented his experience. Some years ago he performed nephrostomy to induce diuresis in anuria caused by poisoning with corrosive mercuric chloride. This consisted of rapid decapsulation and nephrostomy; the incision was made parallel and just posterior to the convex border of the kidney, and gauze saturated with 10 per cent solution of sulphonated bitumen in glycerin was packed through the wound into the renal pelvis. Although the two patients on whom the operation was performed died, the procedure proved its worth in establishing excretion of urine, which excretion continued up to the time of death.

The main indications for nephrostomy, as given by Cabot and Holland, are the presence of obstruction which cannot be satisfactorily remedied by some other method, namely: (1) acute obstruction, either of both ureters or of the remaining ureter, as in anuria caused by calculus or in malignant disease obstructing the ureter; (2) hydronephrosis, or infected hydronephrosis, in which the cause of obstruction may be removable but in which drainage of the kidney as a temporary measure is indicated to improve function; (3) renal calculi with badly injured kidneys; (4) carcinoma of the bladder in cases in which cystectomy is occasionally thought suitable; (5) failure of the musculature of the pelvis, ureters and bladder to evacuate urine, and (6) renal infection without high grade obstruction, in which case nephrostomy is performed to avoid renal infection and to allow recovery.

Livermore reported that in his cases the indications for nephrostomy had been: anuria from the acute nephritis of mercurial poisoning (3 cases); anuria due to stricture of the ureter (1 case); failing renal function from obstruction of the ureter due to ureteral calculi (2 cases),

<sup>16</sup> Livermore, G. R.: Nephrostomy. *Tr. Am. A. Genito-Urin. Surgeons* 26: 37, 1933; discussion on Gutierrez.<sup>15</sup>

and infected hydronephrosis in one functioning kidney due to kinking of the ureter (1 case). The technic employed was as follows: The kidney was exposed and freed if possible. The method of Cabot, namely, opening the pelvis and passing a U-shaped sound into this opening and out through the cortex at a point that satisfactorily drains the lower calix, is excellent; when the kidney cannot be freed, however, an opening may be made in the convex border or on the posterior surface of the kidney, and the pelvis entered. Livermore stated that he had not used the winged catheter advocated by Cabot but had relied on a number 22 to 35 French catheter, cutting off its tip so as to have an opening in the end. The catheter may be retained in the pelvis by suture to the capsule of the kidney with number 2 plain catgut sutures and anchored to the skin by two sutures of silkworm gut. When the sinus has been well formed a new tube may easily be inserted and held in place by strips of adhesive tape through a safety-pin in the tube. All these patients have symptoms of uremia, and most of them are very anemic. All measures for the promotion of diuresis must therefore be instituted. Transfusion of whole blood not only improves the patient's general condition but also increases the renal function.

Livermore stated that nephrostomy preliminary to secondary nephrectomy should prove of value in selected cases as it is often a life-saving procedure. In the anuria caused by obstructions of the ureter, either bilateral or in the ureter of a single kidney, which cannot be relieved, and in the anuria of acute poisoning by corrosive mercuric chloride, or when the condition of the patient precludes any lengthy operation, nephrostomy can be quickly performed. It is not necessary to free the kidney; exposure of the posterior surface or of the convex border makes it possible to incise the kidney and to pass a tube into its pelvis. The tube should be anchored to the capsule of the kidney with plain number 1 catgut and to the skin with silkworm gut. In some cases it is not unusual to note urine dripping from the tube before the patient leaves the operating room; patients in whom this occurs are particularly benefited by nephrostomy.

*Obstructing and Inflammatory Lesions.*—Walters<sup>17</sup> stated that emergency operations on the kidneys and ureters are usually performed because of obstructing lesions interfering with the adequate passage of urine. The association of renal infections with obstruction produces symptoms characteristic of toxemia, the result of pyelovenous back-flow or of absorption of toxins and bacteria from severe cortical infections, usually with abscesses. Striking examples of restoration of renal

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17. Walters, Waltman: Acute Obstructing and Inflammatory Lesions of the Kidneys and the Ureters, *Ann. Surg.* 98:789 (Oct.) 1933.

function after the removal of renal and ureteral calculi and complete drainage of the kidney by temporary nephrostomy are convincing arguments in favor of using such conservative methods of caring for the lesions rather than resorting to treatment by nephrectomy. This is true in most cases even when there is considerable infection within the renal pelvis (infected hydronephrotic sac) and, occasionally, within the renal parenchyma. If a kidney is producing general evidence of severe infection and toxemia, however, and the opposite kidney is normal, immediate removal of the affected kidney is usually essential to recovery of the patient.

Walters stated that one normally functioning kidney will maintain adequate renal function in the presence of complete obstruction of the other kidney; thus, any evidence of renal insufficiency in such cases indicates that the function of the other kidney is not adequate. There are a few exceptions to the rule, but when there is doubt, nephrostomy rather than nephrectomy is the advisable procedure.

Walters stated further that perinephric abscess is characterized by a typical clinical picture consisting of pain in either renal area, fever, leukocytosis, tenderness to pressure and in most cases scoliosis with obliteration of the line of the iliopsoas muscle evident on roentgenologic examination. In such cases surgical exploration of the perirenal region is always advisable. Intrarenal hemorrhage that requires emergency surgical procedures is rare, but it may develop in cases in which there is traumatic fracture of the kidney or of its vessels or, although rarely, following operation on the kidney.

Braasch<sup>18</sup> noted that adequate drainage can frequently be established by means of the ureteral catheter. Nephrostomy or pyelostomy also gives the desired drainage. If an acute cortical infection is present, however, neither drainage by catheter nor nephrostomy will correct the condition, and immediate nephrectomy is advisable. If on exploration many small abscesses are found scattered over the entire kidney and if the other kidney is similarly affected the question whether nephrectomy would be advisable may well be asked.

The clinical diagnosis of cortical infection may be difficult. Often the evidence of toxemia is the best guide. The patient has a toxic appearance and complains of headache and stupor. There may be no localized tenderness or pain in the region of the affected kidney. In doubtful cases it would be a conservative procedure to remove the kidney in order to prevent the possibility of secondary infection of the other kidney by way of the blood stream. This course would be preferable to waiting until the other kidney becomes involved, a condition which

18. Braasch, W. F., in discussion on Walters.<sup>17</sup>

would be shown by an increase in the blood urea. At necropsy, cortical infection is usually found in the other kidney, and often such an infection would not have developed if the primarily infected kidney had been removed earlier.

Braasch mentioned another phase of the problem, brought out by Walters in demonstrating how dependent one is on intravenous or excretory urography. For various reasons the general surgeon has been slow to adopt this most valuable adjunct in the diagnosis of renal conditions. One reason may be that he regards urography as being within the exclusive province of the urologist. Braasch does not think that it is. Intravenous urography is a method of general diagnosis, and it should be employed more often, as it undoubtedly will in the future. The only difficulty is the matter of interpretation; with increasing familiarity with interpretation of the intravenous urogram, however, the method will be employed in routine differential diagnosis of abdominal disease. More and more diagnoses are being made by the country practitioner by means of this invaluable method. It has proved of great value in the evaluation of postoperative results. Braasch warned, however, that one should not expect too much from intravenous urograms made within a week or ten days after operation on the kidneys. A reflex inhibition of excretion often persists for several weeks. If urograms are taken two weeks or a month later most interesting data which could be acquired in no other way are often available.

Intravenous or excretory urography is of great value to the surgeon in interpreting roentgenographic shadows, in determining the position of the stone in the kidney and in ascertaining the function of both kidneys. Next in importance is the aid it gives in the demonstration and visualization of stasis; in this respect it is unquestionably of great value to general practitioners. It is also of great value in injuries of the kidney. From the evidence of extravasation of urine into the surrounding tissues it is possible to determine not only when rupture of the kidney is present, but also its degree. Rupture of the bladder is much better demonstrated by means of the intravenous cystogram than in any other way. Thus the danger of ascending infection from catheterization is avoided.

Beer<sup>19</sup> stated that it is well known that a stone in the ureter may inhibit renal function. A catheter passed up to the stone may fail to collect a specimen of urine and give the impression that the kidney is definitely not functioning; as a matter of fact, in many of these cases an intravenous urogram may show that there is no function. Not knowing this, the general surgeon may operate on the kidney to inspect

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19. Beer, E., in discussion on Walters.<sup>17</sup>

it, and perhaps remove it. Beer believed that the rational procedure in cases of so-called "resting kidney," or "hibernating kidney," was to remove the obstructing stone. He did not believe that the kidneys were resting or hibernating; on the contrary he believed that they were secreting all the time, although one could not collect a specimen. He said that in every abdominal condition in which the diagnosis is not clearcut, a flat plate roentgenogram, an intravenous urogram and a series of tests of the gallbladder and of the gastro-intestinal tract should be made.

*Typhoid Infection.*—Huggins and Roome<sup>20</sup> reported 2 cases in which the patients were carriers of chronic urinary typhoid infection and had pyonephrosis with calculi. In both cases a cure was obtained by excision of the pyonephrotic kidney. The importance of a complete urologic examination of these carriers is emphasized.

#### URETER

*Tumors.*—Colston<sup>21</sup> reported a case of primary papillary epithelioma of the ureter in which existed the hitherto unreported complication of implantation of the tumor in what probably was a preexisting diverticulum of the bladder. The treatment consisted primarily of nephrectomy, which was followed by complete ureterectomy nine months later when the correct diagnosis was made. Six months after the second operation the diverticulum containing the implant was removed. The correct diagnosis was not made until persistent bleeding from the ureter was discovered on cystoscopic examination and the ureterogram presented a typical picture. Colston also reported 2 other cases from the records of the Brady Urological Institute, in both of which the patients died.

The value of the diagnostic syndrome of Chevassu and Mock, obstruction to the passage of a ureteral catheter followed by a copious flow of blood from the ureteral orifice, and the great importance of the ureterogram are emphasized. Complete nephro-ureterectomy is the method of choice, and all observers who have written on the subject say that it should be employed in all the cases in which the condition of the patient permits. The inadequacy of many methods of so-called complete nephro-ureterectomy is emphasized, as the mucous membrane of the distal stump of the ureter is not removed or destroyed by those methods. The extreme importance of complete eradication or destruction of the ureteral mucous membrane, especially in the intramural portion of the ureter where implantation of a tumor has been shown to

20. Huggins, C. B., and Roome, N. W.: Typhoid Pyonephrosis: Its Urological and Public Health Significance, *J. Urol.* **31**:587 (April) 1934.

21. Colston, J. A. C.: Primary Tumors of the Ureter. *Tr. Am. A. Genito-Urin. Surgeons* **26**:65, 1933.



occur, is emphasized. A method of complete ureteronephrectomy is reported, combining the previously well known steps but adding the hitherto unreported technic by which the mucous membrane of the distal stump of the ureter is completely destroyed by high frequency current throughout its course through the wall of the bladder.

*Anastomosis.*—Higgins<sup>22</sup> presented a technic for simultaneous bilateral transplantation of the ureters into the rectosigmoid colon. In his method the continuity of the ureter is not interrupted until the new channel develops, and the normal physiologic function of the upper part of the urinary tract is not altered until the anastomosis has formed. The simplicity of the procedure allows the operation to be performed on a child with exstrophy of the bladder, before the development of renal complications. Higgins reported a case in which a boy, aged 4 years, underwent such an operation and in which a most satisfactory result was obtained with only a slight postoperative reaction. Examinations of the kidneys and ureters of dogs have been made six months after this operation, and evidence of hydronephrosis or of infection has not been observed. Higgins stated that experience with animals has shown that following this procedure peritonitis, shock and acute renal sepsis are reduced to a minimum.

*Injury.*—Stevens<sup>23</sup> stated that injury to the ureter is a serious complication which results disastrously in a large percentage of cases, especially if it is not recognized during the operation. The left ureter is injured more frequently than the right during pelvic operations, incision being the most common type of ureteral accident. A ureterovaginal fistula is the usual sequel to ureteral injury. Although a normal ureter is never perforated by an ordinary ureteral catheter, this accident may occur if the ureteral wall has been injured by some preceding pathologic condition. The use of wire stylets should be abandoned. Operation is not necessarily required following perforation or rupture of the ureter.

In certain types of operation, such as hysterectomy for carcinoma, removal of large pelvic growths, and when difficulty is anticipated because of adhesions or other abnormal conditions, the insertion of ureteral catheters before operation is a time-saving procedure, aiding in the detection of the ureters and insuring them against injury.

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22. Higgins, C. C.: Aseptic Ureterointestinal Anastomosis, *Am. J. Surg.* **22**: 209 (Nov.) 1933.

23. Stevens, W. E.: Accidental Operative Injuries of the Female Ureter, *J. Urol.* **31**:741 (May) 1934.

(To be concluded.)

# ARCHIVES OF SURGERY

VOLUME 29

NOVEMBER 1934

NUMBER 5

## PASSIVE VASCULAR EXERCISES

TREATMENT OF PERIPHERAL OBLITERATIVE ARTERIAL DISEASES BY  
RHYTHMIC ALTERNATION OF ENVIRONMENTAL PRESSURE

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AND

MONT R. REID, M.D.

CINCINNATI

The principal objectives in the treatment of obliterative arterial diseases are the relief of pain and the reestablishment of an adequate collateral circulation in the extremity. The active vascular exercises advocated by Buerger,<sup>1</sup> later modified by Allen,<sup>2</sup> as well as all forms of chemotherapy, physical therapy and surgery, contribute greatly to the patient's comfort. These measures, however, fail to bring about a complete or even an adequate restoration of the circulation in the majority of patients, especially in those suffering from extensive organic disease of the peripheral arteries.

It has long been known that the circulation of a part could be enhanced greatly by decreasing the environmental pressure, thereby decreasing the peripheral resistance to the flow of blood through the part. This principle was first utilized clinically by James Murray,<sup>3</sup> in 1812. Many reports concerning this method of treating acute and chronic inflammatory processes appeared during the past one hundred years. In 1905, Klapp<sup>4</sup> built an apparatus into which an entire extremity could be placed and treated by decreased environmental pressure. He reported excellent results in mobilizing stiffened joints after increasing the vascularization by means of the suction apparatus. In 1908, Willy Meyer and Schmieden<sup>5</sup> published a book entitled "Bier's Hyperemic

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1 Buerger, I.: *Circulatory Disturbances of the Extremities*, Philadelphia, W. B. Saunders Company, 1924.

2 Allen, Arthur W.: *Recent Advances in the Treatment of Circulatory Disturbances of the Extremities*, Ann. Surg. 92:931, 1930.

3 Murray, James: *Nature and Treatment of Cholera: New Method Proposed*, London M. & S. J. 1:749, 1832; 2:185, 1832; *On the Local and General Influence on the Body of Increased and Diminished Atmospheric Pressure*, Lancet 1:909, 1835.

4 Klapp, R. *Mobilisierung versteifter und Streckung kontrakturer Gelenke durch Saugapparate*, München. med. Wchnschr. 52:796, 1905.

5 Meyer, W., and Schmieden, V.: *Bier's Hyperemia Treatment*, Philadelphia, W. B. Saunders Company, 1908.

"Treatment," in which they described and illustrated Bier's apparatus for bringing about an increase in the circulation in the extremities by means of suction. In 1917, Sinkowitz and Gottlieb<sup>5a</sup> reported excellent results in thrombo-angiitis obliterans with Bier's suction hyperemia treatment. In 1928, Dennis Jackson<sup>6</sup> of the department of pharmacology of the University of Cincinnati designed and built a special metal boot, with small windows in it, for the application of suction to the lower extremities, but as far as can be determined the boot was never used for clinical purposes. Braeucker<sup>7</sup> published an interesting article on the treatment of Raynaud's disease by creating a partial vacuum about the affected extremity. He illustrated and described his apparatus in detail, and reported excellent results from this form of treatment in nineteen patients with Raynaud's disease. He stated that the patients remained free from symptoms after from four to eight weeks of intensive treatment.

In August 1932, we<sup>8</sup> completed an apparatus with which we were able to create an environment of intermittent negative pressure about an extremity. That apparatus was constantly modified and improved until, in February 1933, we constructed the original Pavaex research unit. The apparatus is entirely automatic, and will rhythmically change the pressure within the treatment chamber to any selected degree and at any selected rate of alternation. It was through the use of the automatic apparatus<sup>9</sup> for over a thousand treatments that we were able to collect sufficient clinical and experimental data to prove beyond doubt that the rhythmic exchange of pressure from about 80 mm. of mercury negative pressure to about 20 mm. of mercury positive pressure is responsible for the development of an adequate collateral arterial circulation. In the last analysis the treatment consists of passive vascular exercises, which, when carried out frequently enough, cause the smaller arterioles to dilate and become sufficiently large to carry on the collateral circulation about the obliterated or badly diseased arteries.

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5a. Sinkowitz, S. J., and Gottlieb, I.: Thrombo-Angiitis Obliterans: The Conservative Treatment by Bier's Hyperemia Suction Apparatus, *J. A. M. A.* **68**: 961 (March 31) 1917.

6. Jackson, Dennis E.: Personal communication to the authors, July 7, 1932.

7. Braeucker, W.: Die Behandlung der Raynaudschen Krankheit, *Chirurg.* **3**:756 (Sept. 1) 1931.

8. (a) Reid, Mont R., and Herrmann, Louis, G.: Treatment of Obliterative Vascular Diseases by Means of an Intermittent Negative Pressure Environment, *J. Med.* **14**:200 (June) 1933. (b) Herrmann, Louis G., and Reid, Mont R.: The Pavaex (Passive Vascular Exercises) Treatment of Obliterative Arterial Diseases of the Extremities, *J. Med.* **14**:524 (Dec.) 1933.

9. Prior to the use of this automatic apparatus the manually controlled unit, as described and illustrated in previous publications, was used for over two thousand and six hundred treatments. The basic principle is the same in both types of apparatus.

In February 1933, Landis and Gibbon<sup>10</sup> published a preliminary note on the effects of alternate suction and pressure on the circulation in the lower extremities of a normal subject. They employed from 100 to 120 mm. of mercury negative pressure for twenty-five seconds, followed by from 80 to 120 mm. of mercury positive pressure for five seconds. The skin temperature was measured to detect changes in the blood flow. Landis<sup>11</sup> later stated that they were gathering some interesting and important data concerning the actual increase in the blood flow as brought about by the method of alternate suction and pressure. Until that time, however, they had confined themselves to the problem of discovering the most efficient method of applying negative and positive pressure, with the plan to use that information later in the treatment of patients. Such fundamental physiologic studies will undoubtedly place this form of treatment on a sound scientific basis.<sup>11a</sup>

#### THE PAVAEX (PASSIVE VASCULAR EXERCISE) APPARATUS

For the purpose of studying the effect of various amounts of negative and positive pressure and various rates of alternation on all forms of obliterative arterial diseases we designed and built an apparatus which we called the Pavaex research unit. The apparatus (fig. 1) consists of a control box and a chamber into which the extremity is placed. A specially constructed door on one side of the treatment chamber is designed to permit calorimetric and oscillometric studies to be made while the extremity is subjected to various amounts of negative or positive pressure. The construction of this chamber has been described in detail in previous publications.<sup>12</sup> The control box (fig. 2) of the unit houses all the mechanical and electric equipment necessary for the automaticity of the alternation of pressures. The unit was designed for the treatment of several patients at one time (capacity for six patients); consequently, separate sources of suction and pressure have been provided. In the Vascular Disease Clinic of the Cincinnati General Hospital the source of suction is a Worthington vacuum pump, with a capacity of 10 cubic feet (0.28 cubic meter) of air per minute at 26 inches (66.04 cm.) of mercury negative pressure. The pressure is supplied from the compressed air line of the hospital. The pressure and suction lines are connected to the control box by flexible heavy rubber tubes. The flexible tube to the treatment chamber passes out the opposite side of the control box.

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10. Landis, E. M., and Gibbon, J. H.: Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities, *Proc. Soc. Exper. Biol. & Med.* **30**:593 (Feb.) 1933.

11. Landis, E. M.: Personal communication to the authors, May 16, 1933.

11a. Since this article was written a report of the important work of Landis and Gibbon has appeared in the *Journal of Clinical Investigation*. Reference will be made to that work in a subsequent publication.

12. Herrmann, Louis G.: Syphilitic Peripheral Vascular Diseases: Treatment by Means of an Intermittent Negative Pressure Environment, *Am. J. Syph.* **17**: 335 (July) 1933. (b) Reid and Herrmann.<sup>5a</sup> (c) Herrmann and Reid.<sup>5b</sup>

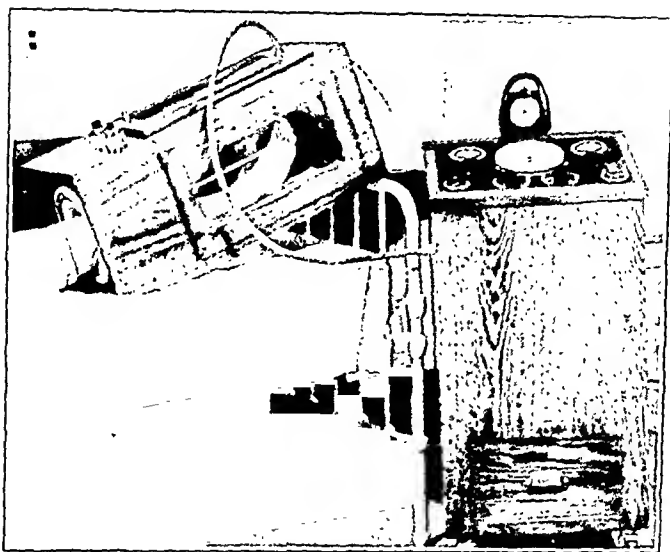


Fig. 1.—The original Pavaex Research Unit connected with the treatment chamber. Note that the extremity is elevated several inches above the level of the patient's heart.

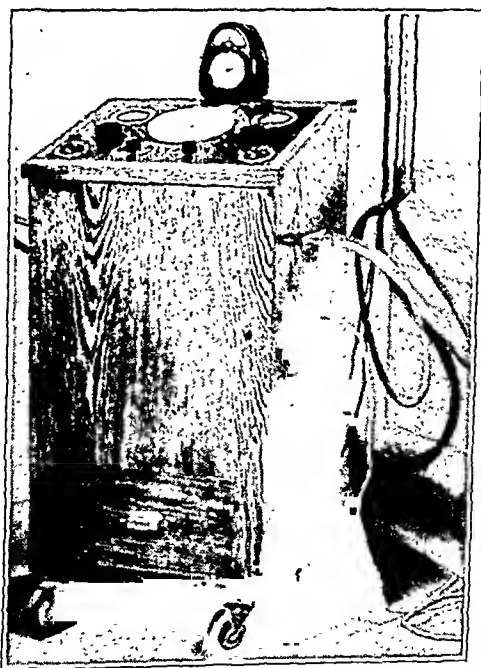


Fig. 2.—The control box of the original Pavaex apparatus, showing the connections with the main supply of negative and positive pressure.

The control panel (fig. 3) carries the following objects: the dial in the upper left-hand corner which shows the amount of suction present in the main system at all times; the corresponding dial on the opposite side showing the amount of pressure present in the main system at all times; the knob below the suction dial which controls the rate at which air is withdrawn from the treatment chamber; the corresponding knob on the other side which controls the rate at which air is permitted to enter the treatment chamber; the large dial in the center which shows exactly the amount of positive or negative pressure existing within the treatment chamber at all times; the main switch on the left which controls the supply of current to the control box, and the corresponding switch on the other side which controls the current to the electric motor which drives the vacuum-pump.

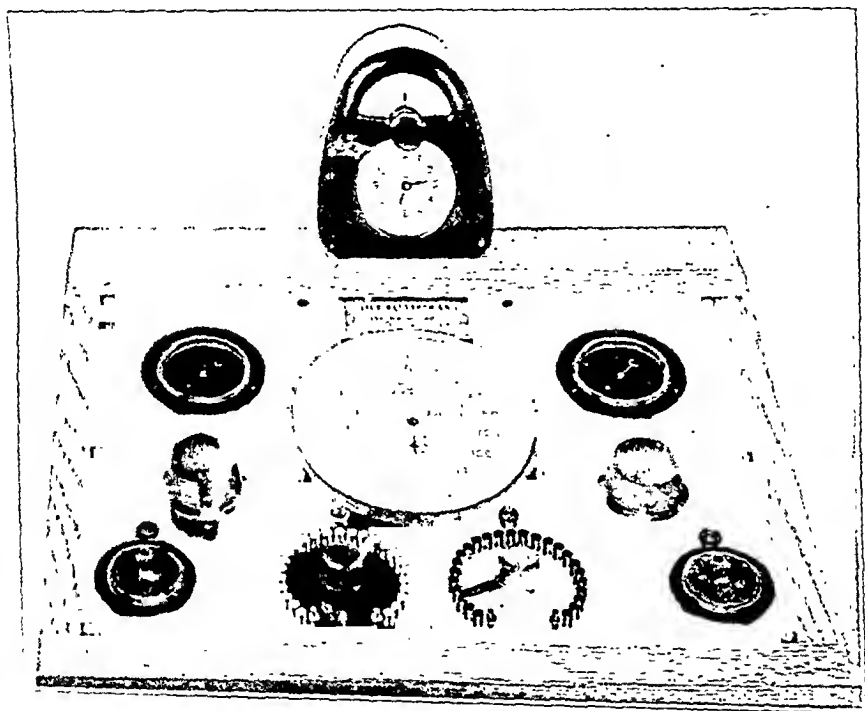


Fig 3.—The control panel of the original Pavaex apparatus. The large dial in the center shows the actual amount of negative or positive pressure which is present in the treatment chamber at all times during the treatment.

An amber light is connected in each of the circuits in order that one can be certain at a glance that the current has been turned on and the apparatus is ready to function. The two sets of contact-points are the selectors for negative and positive pressure, respectively. With them it is possible to produce any amount of positive or negative pressure within the treatment chamber from 5 to 120 mm. of mercury in steps of 5 mm. of mercury. When there is negative pressure in the treatment chamber a green light is energized, while a red light is energized when the pressure changes to the positive side. An electric interval clock is mounted on the control box in order that the rate of alternation and the duration of the treatment can be determined accurately. The apparatus is efficient and accurate and can be operated by a trained assistant. The patients who have been treated

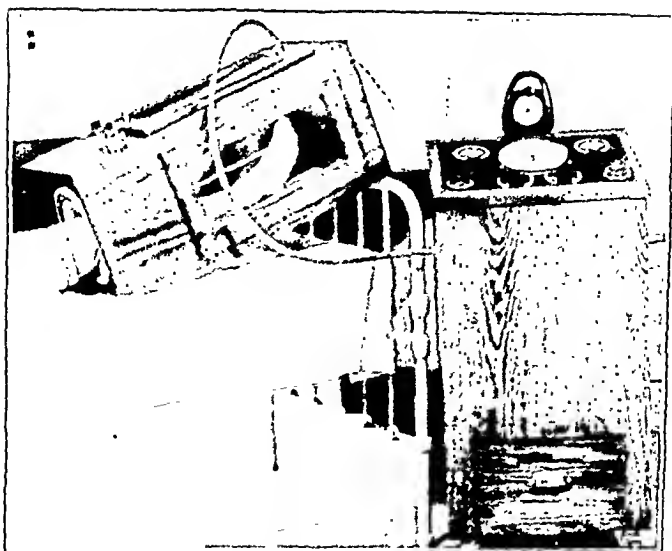


Fig. 1.—The original Pavaex Research Unit connected with the treatment chamber. Note that the extremity is elevated several inches above the level of the patient's heart.

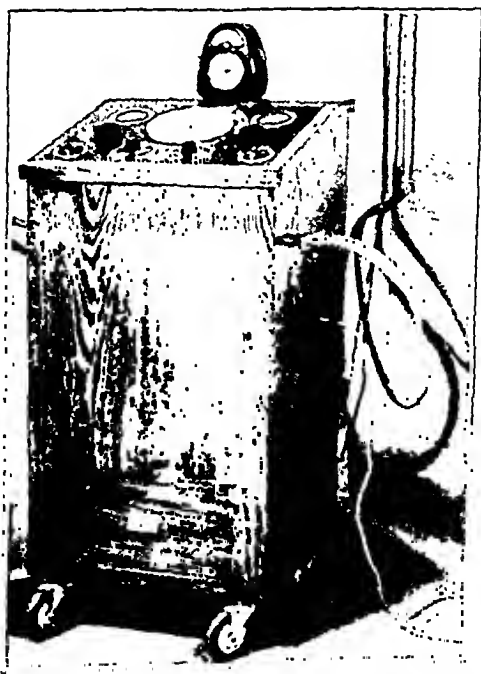


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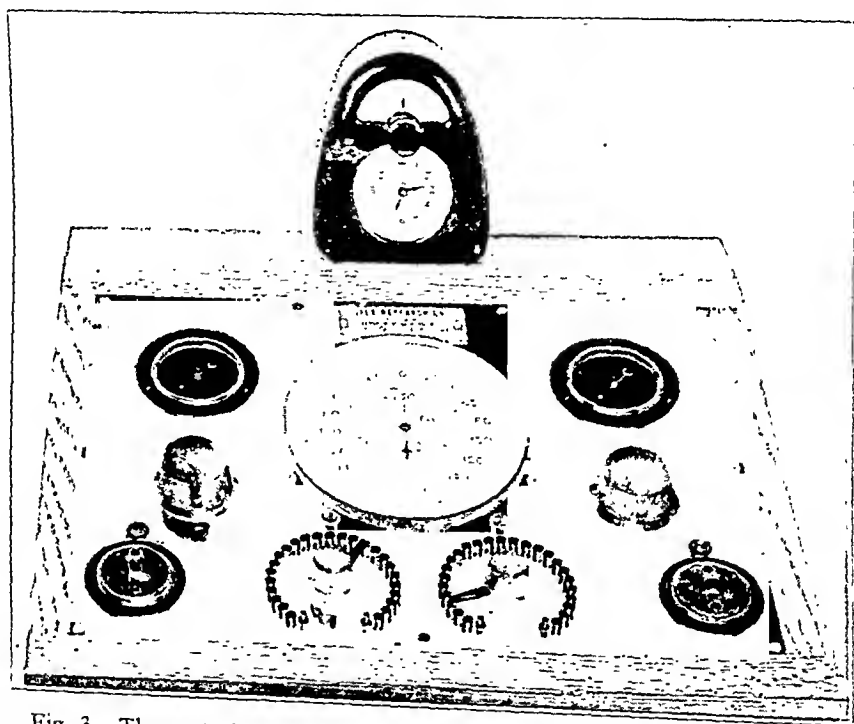


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exclusively by this apparatus have shown a rapid improvement in both subjective and objective findings. A simpler form of the apparatus is being manufactured commercially,<sup>13</sup> so that adequate treatment can be given in the home, office or small hospital.

#### METHOD OF TREATMENT

The patient is placed on a bed or cot, and the extremity to be treated is inserted through a soft rubber cuff into the treatment chamber (fig. 1). Large windows are so arranged that the color of the foot and leg can be observed at all times. A small amount of soap is rubbed on the inside of the glass windows, and the glass polished with a soft, dry cloth, so that moisture will not collect on the glass during the treatment. The foot and leg are then elevated several inches above the level of the heart. The treatment chamber is connected to the control box by means of a thick-walled rubber tube. The two main switches on the control panel are turned on, and the selector switches set for 80 mm. of mercury negative pressure and 20 mm. of mercury positive pressure. The rate of alternation is controlled by the knobs just below the main suction dial and main pressure dial on the control panel (fig. 3).

The apparatus automatically changes the pressure within the treatment chamber from the selected amount of negative pressure to the selected amount of positive pressure and at the rate of alternation desired. The average rate of one such cycle is about fifteen seconds. It has been our experience that in patients with high degrees of obliteration the first few treatments should be given with the alternation requiring about one half minute for completion of the cycle. As the circulation improves the rate of alternation is slowly increased until the entire cycle takes place within about fifteen seconds. For patients with extensive obliterative vascular disease with impending gangrene of the distal portions of the extremity we believe that it is necessary to hospitalize the patient and give four or five treatments (lasting for twenty minutes each) every day until the circulation of the foot shows definite signs of improvement. In our experience, striking changes in the circulation become established after two weeks of such intensive treatment. For the patient with intermittent claudication as the major complaint two treatments each day (for twenty minutes each) give satisfactory results in relieving them of pain and in restoring the circulation to an adequate level.

#### REPORT OF CASES

Fifty-one patients with organic obliterative arterial disease of one or more extremities have received regular and intensive treatment by this method. Thirty-two of these patients had a high degree of peripheral (senile) arteriosclerosis without evidence of gangrene; five had trophic lesions of one or more toes together with moderately severe diabetes mellitus; six had extensive organic arterial disease of the thrombo-angiitis obliterans type, and all six had one or more gangrenous digits of the hands or feet; four had syphilitic obliterative arteritis of the endarteritic or of the thrombo-arteritic type,<sup>12a</sup> and four had atypical arterial disease of the obliterative type. The clinical diagnosis in all

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13. This apparatus is being manufactured by the Cincinnati Scientific Company, 224 Main Street, Cincinnati.

cases was confirmed by complete vascular studies before and after vasomotor relaxation under controlled conditions of temperature and humidity. Cases of pure vasomotor disturbances have not been included in this series.

Since August 1932, we have given three thousand, seven hundred and sixty-nine treatments by the Pavaex apparatus. Over three thousand of the treatments have been given to the fifty-one patients with organic obliterative arterial disease. Forty-six of the patients required treatment for both lower extremities.

One patient in the group with extensive (senile) arteriosclerosis was seen in consultation with Dr. J. L. Tuechter because of acute arterial thrombosis accompanied by excruciating pain and physical signs of marked ischemia of the right foot and leg. Complete vascular studies showed that the occlusion was organic and not the result of vasospasm. The patient was treated vigorously for periods of twenty minutes five times each day for two weeks, in the meantime being kept at complete rest in the hospital. The circulation improved rapidly, and the pain disappeared after three days of treatment. After about five days the toes retained the normal pink color between treatments. The patient was able to lie flat in bed with his lower extremities on the level with his heart after seven days of treatment. After leaving the hospital the patient continued to receive treatments at irregular intervals, but never more than one week apart, for three months. Recently he went hunting, walking for several hours without experiencing real discomfort. The severe intermittent claudication which was always present after slight exertion before the treatments were given has been completely relieved.

It is difficult, at present, to express in mathematical terms the benefits which have been derived from this form of therapy. The multiplicity of signs and symptoms (discoloration of the toes, subjective and objective sensation of cold extremities, aching or burning pains in the feet, easy fatigue of the muscles of the extremities, pain in the feet while at rest or intermittent claudication) which are directly or indirectly the result of organic disease of the peripheral arteries accounts in part for this difficulty. A careful analysis of the results obtained in the fifty-one patients reported in this work gave us the following data: In all the patients who received intensive treatment for two weeks or longer there was a definite increase in the surface temperature of the extremity when observed under controlled conditions of temperature (20 C. [68 F.]) and humidity (50 per cent). Forty-four of the patients (86.27 per cent) stated that most of the pain disappeared after about twenty-five treatments of twenty minutes each extended over a period of about two weeks. Six patients (11.76 per cent) showed only slight symptomatic relief after more than two months of treatment. One patient (1.97 per cent) stated that the pain was not influenced by three months of treatment, and no other cause for the patient's pain could be found. Four patients with moderately severe peripheral arteriosclerosis who were treated three times a week for

eleven weeks stated repeatedly that definite subjective and objective evidence of an increase in the circulation in the extremities remains for about forty-eight hours after each treatment. We are not prepared to give any information concerning the permanency of this increase in the circulation. We are, however, of the opinion that this form of treatment should be carried out over a period of many months if a permanent increase in the circulation is to be established.

It is highly important that patients with organic disease of the peripheral arteries continue to practice those measures for the general care of the feet which have been repeatedly emphasized by Allen<sup>2</sup> and by Reid.<sup>14</sup> Treatment with the Pavaex unit should supplement the methods which experience has shown to be of utmost importance in preventing infection from entering into the poorly nourished tissues of patients with peripheral vascular diseases. Forthcoming publications will give detailed reports concerning the results of treatments with the Pavaex unit in other types of obliterative arterial diseases.

#### SUMMARY

All therapy for obliterative vascular diseases should be directed primarily toward the establishment of a collateral circulation of sufficient magnitude to furnish proper nourishment to the distal portions of the extremity.

Rhythmic alternation of the environmental pressure about an extremity can be brought about automatically by the Pavaex apparatus.

The Pavaex treatment is essentially a mechanical means of performing passive exercises of the vascular system, i. e., passive vascular exercises.

A total of three thousand, seven hundred and sixty-nine treatments with the Pavaex unit have been given up to July 1933. Over three thousand of the treatments have been given to the fifty-one patients reported in this article.

Calorimetric evidence of an increase in the circulation in the distal parts of the extremities occurred in all fifty-one patients of the series, yet 13.73 per cent received little or no relief from their symptoms.

Forty-four patients (86.27 per cent) were greatly benefited by this form of therapy.

We believe that treatment with the Pavaex unit (passive vascular exercises) is the most effective means of bringing about the development of an adequate collateral circulation in the extremities of patients with extensive organic obliterative arterial disease.

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14. Reid, Mont R.: The General Care of Peripheral Vascular Diseases, *Ann. Surg.* 96:733, 1932.

# THROMBOSIS OF THE SIGMOID OR LATERAL SINUS

## REPORT OF THIRTY CASES

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DETROIT

AND

S. J. CROWE, M.D.

BALTIMORE

There is a difference of opinion in this country and in Europe regarding treatment of otitic sinus thrombosis. Dandy<sup>1</sup> questioned the necessity for ligation of the jugular vein or an attempt to remove an infected clot. Mygind<sup>2</sup> reported his results in two groups of patients with otitic sinus thrombosis who were treated by different methods. The first group included 98 patients observed during the period from 1915 to 1922, with recovery in 55 per cent. The treatment of these patients was: (1) diagnostic puncture of the infected sinus, (2) removal of the thrombus and (3) ligation of the jugular vein. Mygind's second group of 101 patients observed during the years from 1923 to 1930 were treated more conservatively, and 71 per cent recovered. In 93 of the 101 patients the infected mastoid cells were thoroughly opened, but nothing was done to the sinus or vein: 70 of these 93 patients recovered without further surgical measures. On the other hand, Portmann<sup>3</sup> reported from Bordeaux that cases observed in a five year period showed 100 per cent of recoveries. When the clinical symptoms suggest a sinus thrombosis, Portmann (1) cleans out the mastoid, (2) ligates the jugular vein, (3) removes the clot and (4) obliterates the lumen of the sinus, even when the part of the sinus wall exposed at operation looks normal. During the past twenty years only 30 patients with otitic sinus thrombosis have been treated at the Johns Hopkins Hospital, and an analysis of the symptomatology and end-results in this group clearly shows that each patient must be studied as an individual, and that no dogmatic set of rules for either diagnosis or treatment is justifiable. The small number of cases in our series also illustrates the infrequency of this complication in Baltimore, since an average of 15,000 patients with diseases of the

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From the otolaryngologic service of the Johns Hopkins Hospital.

1. Dandy, W. E., in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 441.

2. Mygind, S. H.: *Treatment of Orogenic Sepsis and Sinus Thrombosis*, *Acta otolaryng.* 16:474, 1931.

3. Portmann, G.: *Considérations sur le traitement de phlébites et thrombo-phlébites sinuso-jugulaires*, *Rev. de laryng.* 52:523 (Oct. 15) 1931.

nose, throat and ear are seen in a year in the outpatient department of this hospital.

In our series of 30 patients with proved thrombosis of the lateral or sigmoid sinus, 66 per cent recovered. More than half of the group (16) were children under 14 years of age. The youngest patient was an infant, aged 1 year, and the oldest was 64. There was a history of acute otitis media in every patient. In the majority the onset of symptoms began with an earache two or three weeks before admission to the hospital. In 9 patients, however, a chronic suppurating otitis media had been present for several years, and a cholesteatomatous formation was probably responsible for the complications. A simple mastoid operation on 3 of the patients had failed to stop the purulent discharge from the ear, and it is possible that a more radical operation when the cholesteatoma first appeared would have prevented the infection of the sigmoid sinus. We feel that as a general rule a cholesteatoma should be treated radically, but the destruction of useful hearing in an attempt to cure a chronic discharging ear and thus prevent possible complications is not justifiable. In the great majority of our patients the sinus thrombosis was a complication of acute otitis media and mastoiditis. In 4 cases there is a note in the history stating that a definite cholesteatoma was present in the mastoid; 3 of the patients were adults over 33 years of age, and one was a child, aged 3 years.

For diagnostic purposes the following points should be noted:

1. A septic temperature was present in only 20 of our 30 cases. In a patient who recovered the temperature varied from 97 to 107.2 F. before operation. In several patients who recovered with no complications the temperature remained septic for as long as a week, and chills continued from two to five days after the operation on the mastoid, the excision of a portion of the sinus wall overlying the thrombus to provide drainage, partial removal of the thrombus and ligation of the jugular vein.

2. Shaking chills or chilly sensations were observed in 15, or 50 per cent, of our 30 patients. It is worthy of note: (1) that 7 (44 per cent) of the 16 children under 14 years of age had chills and (2) that 13 (87 per cent) of the 15 patients who had chills completely recovered, while only 7 (47 per cent) of the 15 patients who did not have chills recovered. This indicates that chills in a general septicemia may be a favorable prognostic symptom.

3. A positive blood culture is of decisive diagnostic value, but a negative culture does not rule out a sinus thrombosis. In our series blood was taken on admission from an arm vein in 21 patients. A culture gave no growth in 12 cases and positive results in 9. Postoperative blood cultures were made in 23 cases and were positive in 12. The hemolytic

streptococcus was the organism most frequently found (15 cases); a nonhemolytic streptococcus was found in 2 cases; the pneumococcus type III was found in 1 case, and the proteus bacillus in 1 case in which the blood was aspirated directly from the infected sinus. These results suggest that the constitutional symptoms (chills and septic temperature) may in some instances be due to absorption of toxins, and that the operative manipulations may disseminate organisms from the original focus.

4. The eyegrounds were examined in 26 patients. No change was noted in 9 patients, and a fulness of the veins in 5, but definite changes, varying from a haziness of the outlines of the nasal margin of the disk with distended veins to a swelling of 4 diopters, were found in 12 patients. The choked disk was limited to the side with the infected ear in 2 patients and was bilateral in 10. The changes in the fundus when bilateral are probably due to increased intracranial pressure and when unilateral to an extension of the infection through one or both of the petrosal sinuses to the cavernous sinus. The presence of either a bilateral or a unilateral choked disk is not necessarily a serious sign, since 4 of our patients with bilateral choking and 1 with unilateral choking recovered after the infection in the mastoid and in the sinus was drained.

5. A lumbar puncture for diagnostic purposes was limited as far as possible to patients with clinical signs of meningitis. The use of lumbar puncture and pressure on the jugular veins to locate the site of the thrombosis is associated with a certain amount of risk of a meningeal infection in patients with general septicemia. In our series of 30 patients only 12 had a lumbar puncture. In 5 the spinal fluid was normal; in 1 there was an increased cellular content with no increase of pressure, and 3 patients had purulent meningitis when admitted to the hospital.

#### REPORT OF CASES

A short résumé of the history and examination of each patient follows, and for convenience the cases are divided into three groups.

Group I comprises 2 patients with chronic suppurative otitis media who had undergone an operation on the mastoid several years prior to the present illness (cases 1 and 2).

CASE 1.—In 1926, L. D., aged 46, had a radical mastoidectomy because of a chronic discharge in the right ear and the formation of a cholesteatoma. The discharge continued without general symptoms until Feb. 2, 1930, when the patient suddenly felt a severe pain in the right ear and the right side of the face; ethmoidal infection was present and was treated locally, but the pain became worse, and on February 8 she had a severe chill with delirium which lasted one-half hour. On the following day she had another chill and was admitted to the hospital; the temperature was 105.2 F. (rectal). Physical examination gave negative results except for a bilateral ethmoid infection and a purulent discharge in the right

auditory canal. The white blood cells numbered 9,800; hemoglobin was 84 per cent. Blood culture on February 11 showed 8 colonies of hemolytic streptococci per cubic centimeter, and three days later 26 colonies per cubic centimeter. The mastoid was opened on February 15, and the lateral sinus was exposed. The sinus was thickened and grayish white. The sinus was opened, and a suppurating thrombus was removed. The internal jugular and anterior facial veins were ligated. Transfusions were given; an infected thrombus of the internal saphenous vein, which suppurated, developed; later pneumonia developed. Convalescence was prolonged, but eventually the patient completely recovered.

CASE 2.—M. B., aged 17, was treated nine years previously for chronic tuberculous infiltration of the lungs, and eight years previously had a simple right mastoidectomy. The patient continued to have intermittent attacks of right otalgia and otorrhea. The illness in question began two days before admission, with pain in the right ear and chills. The severe pain continued, but the discharge from the ear became less. The patient was admitted to the hospital on Oct. 3, 1927. Physical examination gave negative results except for a subperiosteal abscess of the right mastoid. The eyegrounds were normal except for fulness of the veins. The temperature rose to 107.4 F. The white blood cells numbered 16,400, and blood cultures taken on October 3 and 5 were sterile. The abscess was drained on October 3, but the septic temperature continued, and two days later the lateral sinus was exposed. A perisinuous abscess was found, and the lateral sinus was thrombosed. The sinus was opened, and the thrombus removed, but the jugular vein was not ligated. The patient made an uneventful recovery.

Group II comprises 6 patients referred to this hospital with evidence of septicemia following a simple mastoid operation (case 3 to 8).

CASE 3.—In D. M., aged 10 years, following acute tonsillitis acute right otitis media and mastoiditis developed; simple mastoidectomy was done at his home in North Carolina on May 5, 1928, and he was kept under observation in the hospital until the ninth day. Six days later he became drowsy. The temperature was 104 F. The white blood cells numbered 6,000, and malarial parasites were found in the blood, but there was no improvement with quinine therapy. On May 22, a blood culture showed hemolytic streptococci, and on the following day the patient was given a transfusion of 500 cc. of blood. The child was admitted to the Johns Hopkins Hospital on May 28. Physical examination gave negative results. The white blood cells numbered 13,900. The temperature was 104 F. The blood cultures which were taken on May 28 grew hemolytic streptococci. The right mastoid was reopened and the lateral sinus exposed. Pus was found around the jugular bulb; the sinus wall was incised, and the thrombus removed. The internal jugular vein was found collapsed and was ligated. The patient was given transfusions and made an uneventful recovery.

CASE 4.—In D. C., aged 4 years, bilateral acute otitis media developed on April 1, 1928. The drums were incised, and the ears discharged profusely, but the patient did not improve. On April 28 at the local hospital a bilateral simple mastoidectomy was done, but the temperature continued to fluctuate between 99 and 106 F., and there were chilly sensations. On May 8 a blood culture was sterile, and the patient was given a transfusion of 500 cc. of blood. When admitted to this hospital, on May 11, he was irritable. The physical examination gave negative results. The temperature was 102.2 F. The white blood cells numbered 17,500. There were a purulent discharge in the auditory canals and a slight discharge in both mastoid wounds. A culture of the blood grew hemolytic streptococci. The patient

had a chill shortly after admission. The mastoids were reopened, and the lateral sinus was exposed. On the left side the sinus appeared normal, but on the right side a pocket of pus was found near the jugular bulb. The sinus was thrombosed, the wall incised, the thrombus removed and the internal jugular vein ligated. The patient was given transfusions, and on May 24 a culture of the blood showed 20 colonies of hemolytic streptococci per cubic centimeter. An abscess of the hip developed and was incised, which showed *Staphylococcus aureus*. The patient improved and was discharged well.

CASE 5.—J. V., aged 3 years, on April 21, 1924, suddenly felt pain in the right ear. The drum was incised and the ear discharged, but fever continued, and pain developed behind the right ear. On May 18 a simple mastoidectomy on the right was done, and the child improved slightly for four days. The temperature gradually became elevated, and the patient became delirious. Mercurochrome was given intravenously. The temperature became intermittently high and three days before admission a swelling of the right groin developed. The patient was admitted to the hospital very ill and irritable, with poor color; the eyegrounds showed choked disks; the liver was enlarged, and there was an abscess of the left hip and the right ankle. The white blood cells numbered 13,300. The hemoglobin was 48 per cent. The temperature was 103.2 F. A blood culture was sterile. The mastoid was reopened on May 31, and the lateral sinus was exposed and incised, but no thrombus was demonstrable. The internal jugular vein was ligated, and the left drum was incised, with a liberation of pus. The left hip and right ankle were opened and drained. The child remained in a poor condition with a septic temperature. Transfusions were given. A culture of the blood on June 2 was sterile. The patient died on the fourth day. Autopsy revealed a thrombosis of the right lateral sinus.

CASE 6.—V. G., aged 4 years, had a sore throat on May 5, 1928, and pain in the left ear one week later. The drum was not incised, and swelling and redness of the left mastoid region were noted on May 16. Pain and moderate fever continued, and simple mastoidectomy on the left was done on May 20, with some improvement for two days. On May 26 a septic temperature developed, and the child was admitted to this hospital, ill and weak, with bilateral choked disks, a positive Kernig sign and a mastoid wound filled with granulations. The temperature was 105.4 F. The white blood cells numbered 18,200. The blood culture taken on May 26 showed 30 colonies of hemolytic streptococci per cubic centimeter. The mastoid was reopened on the day of admission. The sinus was exposed, incised and found to be thrombosed from above the knee to beyond the subclavian. The thrombus was entirely removed at the upper end, but the lower limit could not be reached. The child grew progressively worse in spite of transfusions. On May 27 a blood culture grew 3,200 colonies of hemolytic streptococci; on May 28, 240 colonies; May 29, 6,000 colonies, and on May 30, 400 colonies; in the last instance the blood was taken immediately following a transfusion. The spinal fluid was clear, with no increase of cells or pressure. Pneumonia developed, and the patient died on June 1, 1928.

CASE 7.—M. D., aged 2½ years, three weeks before admission had influenza and tonsillitis, followed by pain and discharge in the left ear. Two weeks after onset simple mastoidectomy was performed on the left, and after the operation the patient had a septic temperature. A red, swollen area developed on the calf of the left leg, and later the left hip became swollen and tender with fixation and internal rotation. The patient was admitted to this hospital on March 24, 1933, ill and restless. The general examination gave negative results except for the bulging of the left drum; the mastoid wound was open; the right drum was red and full,



and the left thigh was swollen with adduction and internal rotation of the left hip. The temperature was 102.2 F. The white blood cells numbered 25,000. The left hip was incised and drained the following day, and a culture yielded hemolytic streptococci. The mastoid was reopened on March 26, the lateral sinus was exposed and incised, and a partial thrombus was removed; the internal jugular vein was ligated and cut. The patient grew progressively worse. A blood culture on April 2 grew hemolytic streptococci; the spinal fluid showed evidence of meningitis and on culture grew hemolytic streptococci. The patient died on April 3.

CASE 8.—E. E., aged 18, had a simple mastoid operation on the right in 1928, and since then had had an intermittent discharge from the ear. Four weeks before admission a cold in the head and sore throat with delirium and pain and discharge in the right ear developed. She had an oscillating temperature, and the mastoid was opened on March 19, 1933. Chills and a septic temperature developed, and the mastoid was reopened on March 25; the lateral sinus was reported to look normal. When admitted to the Johns Hopkins Hospital on April 1, the patient was sick, thin and undernourished; the skin was dry. Physical examination gave negative results. The temperature was 103 F. The white blood cell count was 5,800; the hemoglobin, 75 per cent. The right mastoid was reopened on April 4, and the lateral sinus was exposed, incised and found thrombosed. The thrombus was removed and the internal jugular vein ligated. This girl had a long convalescence, and was given several transfusions. Repeated blood cultures were sterile.

Group III is composed of 22 patients who were admitted with acute mastoiditis. Subgroup 1 comprises 6 of these patients, whose treatment consisted of a simple mastoidectomy (cases 9 to 14).

CASE 9.—In B. W., aged 7 years, a sore throat developed four weeks before admission, and three days later pain in the right ear. The right drum was incised. Earache developed on the left side three days later, and the left drum was incised. The pain in the left ear persisted, and the discharge was much thicker than that from the right ear. Ten days before admission the child had pain over the left eye and temple and below the left ear, and two days before admission swelling and tenderness of the left mastoid were evident. The child was admitted on Feb. 27, 1932, not acutely ill. Physical examination gave negative results. There was a purulent discharge in the left auditory canal with swelling and redness of the left mastoid. A slight mucopurulent discharge was seen in the right auditory canal. The temperature was 100 F. The white blood cells numbered 14,900. The hemoglobin was 83 per cent. A blood culture was sterile. The left mastoid was opened and found to be filled with pus and granulations, and a large perisinuous abscess was found walled off by granulations. The lateral sinus was thrombosed, but it was not incised. The child made an uneventful recovery.

CASE 10.—M. H., aged 25, was admitted unconscious, with a fracture of the skull and bleeding from the nose and ear. A subtemporal decompression was done on January 26, and nine days later a bloody purulent discharge from the right ear developed, followed in two days by swelling and tenderness of the right mastoid. A simple mastoidectomy on the right was done on February 6, and the lateral sinus was accidentally opened; it bled profusely, and was packed. On February 10 and February 17, blood cultures grew hemolytic streptococci. Spinal puncture revealed a clear spinal fluid. The patient died on February 18, and autopsy showed an infected thrombus of the lateral sinus, septicemia and multiple pulmonary emboli and abscesses.

CASE 11.—W. G., aged 3 years, had acute pain in the right ear three days before admission. The drum was incised, and the ear discharged; two days later a swelling developed in front of and behind the right ear. The patient was admitted on Feb. 28, 1933. Physical examination gave negative results except for edema and swelling above and anterior and posterior to the right ear, with projection of the auricle; the right auditory canal was filled with pus, and there were a pulsating perforation of the drum, large glands at the angle of the jaw and subacute tonsillitis. The temperature was 101 F. The white blood cells numbered 17,300. The subperiosteal abscess was incised and drained on March 3, and the mastoid was opened on March 10. The mastoid was filled with pus, granulations and necrotic bone, and on culture pneumococcus type III was grown. A large perisinuous abscess under pressure was found, and the lateral sinus was thrombosed but not opened. The patient made an uneventful recovery.

CASE 12.—B. M., aged 54, was seen in the dispensary on June 23, 1915, with a complaint of pain in the right temporal, mastoid and occipital regions of five weeks' duration. The right drum was incised, and pus was obtained. The patient had a chronic infection of the right frontal sinus, ethmoids and antrum, perforation of the palate and loss of the greater part of the septum. The symptoms continued, and the patient was admitted on July 6. The ethmoid cells and the right antrum were opened on July 8, and the mastoid was opened on July 13. The mastoid was dense and hard and contained a few small infected cells; the mastoid antrum was filled with pus and granulations. On admission examination revealed nothing except the changes already noted. The white blood cells numbered 7,500. The Wassermann reaction was negative, and examination of the spinal fluid and of a blood culture gave negative results. Following operation the temperature remained elevated; the spinal fluid was normal, and the eyegrounds revealed a choked disk on the right. The patient became irrational and died on August 2. Autopsy revealed necrosis of the right temporal bone and thrombosis of the right sigmoid and lateral sinuses.

CASE 13.—B. W., aged 64, had acute left otitis media eighteen years previous to admission which cleared up with no further trouble. Headaches developed four months previous to admission, and one month later pain in the left side of the head, fever and delirium were manifest. The patient was unconscious for two days. He then had an irregular fever, and weakness of the left arm was evident. Five weeks later he had a second attack with weakness and unsteadiness of gait, which increased; the left ear began to discharge. Five weeks before admission he noticed dimness of vision; he became irritable and emotionally unstable and lost 45 pounds (20.4 Kg.). He was admitted to the hospital on Aug. 7, 1924. Physical examination revealed a slight serous discharge in the left ear, moderate choking of the disks, a small hemorrhage in the left fundus and loss of the right corneal reflex; station and gait were unsteady, and true ataxia and weakness of the left arm were present. The Romberg sign was positive. The white blood cells numbered 10,200. A cerebellar abscess was found and evacuated; on culture it grew *Staphylococcus aureus*. A radical operation was done on the left mastoid on October 1, and a large cholesteatoma which had eroded into the posterior fossa was found; the lateral sinus was thrombosed, but it was not opened. The patient improved for a time, but pneumonia developed, and he died.

CASE 14.—M. M., aged 6 years, acquired a cold in the head and pain in the left ear on Feb. 26, 1925. There was no discharge from the ear. The patient had a high fever at night and became delirious on March 9. The drums were punctured with a needle on March 9 and again on March 12, but the patient had a chill during the evening of March 12 and was admitted to the hospital on

March 13. Physical examination gave negative results, except for bulging drums with a serous discharge from the left canal, marked tenderness of the left mastoid, bilateral choked disks and full veins and dilatation of the cutaneous veins over the forehead. The white blood cells numbered 19,800. The hemoglobin was 60 per cent. A blood culture was sterile, and the spinal fluid was clear, with a slight increase of pressure. The left mastoid was opened on March 14. The cells around the antrum were filled with granulations; the lateral sinus was incised and drained. The patient improved slowly and was discharged on April 3.

Subgroup 2 is composed of 7 patients whose treatment consisted of a simple mastoidectomy and ligation of the jugular vein (cases 15 to 21).

CASE 15.—L. P., aged 4 years, had measles two weeks before admission, and eight days later pain in the left ear, but no discharge. A swelling developed behind the left ear two days before admission to this hospital, April 8, 1931. Examination disclosed a sick girl with acute follicular tonsillitis, a serous discharge in the left ear, a bloody discharge in the right ear and bilateral postaural swelling; the eyegrounds were normal. The temperature was 104 F. The white blood cells numbered 31,200. On April 9, incision and drainage of the subperiosteal abscesses were done. A blood culture was sterile. On April 12, a bilateral mastoidectomy was done, and pus and granulations were found in the mastoids. On the left side a small perforation of the sinus plate and a large perisinuous abscess were found; the sinus wall was collapsed and filled with pus. The thrombus was removed superiorly from the sinus, and the internal jugular vein was ligated. The temperature fell gradually to normal. The patient was given transfusions and had an uneventful recovery.

CASE 16.—R. B., aged 54, had influenza with nausea and vomiting three weeks before admission; these were followed by a severe jumping pain in the left ear and severe headache. The left drum was incised and discharged, and on April 10, 1917, edema of the wall of the canal was noted, and he was admitted to the hospital on April 12. Physical examination gave negative results; the eyegrounds were normal, and there was discharge in the left auditory canal and edema of the posterior wall of the canal. The temperature was 102 F. The white blood cells numbered 12,600. The spinal fluid was clear, and the pressure was increased. A blood culture grew nonhemolytic streptococci, 10 colonies per cubic centimeter. The patient had a chill on April 14, and the mastoid was opened and found to be filled with thin, sticky pus and necrotic bone. The sinus plate was necrotic, and a perisinuous abscess was found. The lateral sinus was incised and bled freely. A mural thrombus was present, and the left internal jugular vein was ligated. The patient made an uneventful recovery, but nonhemolytic streptococci were grown in a blood culture on April 13 (2 colonies) and again on April 24.

CASE 17.—C. C., aged 40, had pain in the right ear four weeks before admission, and the ear discharged pus two days later. Two weeks before admission she had marked nausea, felt hot and chilly at times and complained of a dull, throbbing headache of the right temporal and occipital regions. Following this she began to have dimness of vision, and her friends noted a drooping of the right upper eyelid. She was admitted to the hospital on Jan. 8, 1932. Physical examination gave negative results except for a purulent discharge in the right ear, a full drum with a small posterior pulsating perforation, eyegrounds which showed marked bilateral papilledema, with a few punctate hemorrhages and an exudate about the disks, and drooping of the right upper eyelid. The temperature was 102 F. The white blood cells numbered 15,000. A blood culture grew 1 colony of hemolytic streptococci from 2 cc. of blood. The right mastoid, which was opened on Febru-

ary 12, showed evidence of slight infection; a perisinuous abscess was found around the lateral sinus, which was covered with granulations. The sinus was incised, and the thrombus removed; the internal jugular vein was ligated. The patient convalesced slowly. A blood culture on January 16 grew hemolytic streptococci, less than 1 colony per cubic centimeter. The ptosis of the right eyelid cleared up, and the papilledema subsided.

CASE 18.—B. F., aged 7 years, had had occasional attacks of otorrhea after typhoid fever three years previously, and during the past winter had several attacks of earache with a foul discharge from the ear. On Jan. 6, 1918, pain and discharge developed in the left ear; the patient had chills and fever daily and at night became delirious. He had a chill on January 11 and was admitted to the hospital on January 12. The temperature was 100.2 F. The left auditory canal was filled with a foul, purulent discharge. There were swelling and marked tenderness of the left mastoid and fullness and tenderness along the left internal jugular vein. The head rotated to the right; the muscles of the neck were spastic and the Kernig sign was positive. The patient was drowsy. The white blood cells numbered 26,200. A blood culture was sterile. Spinal puncture revealed a clear fluid, with a normal pressure and 20 cells. The left mastoid was opened on January 12 and found extensively involved; all of the bone was necrotic. A perisinuous abscess was found, and the wall of the sinus was nowhere intact. The lumen was filled with pus. An extradural abscess was found posterior to the sinus, and 1 ounce (31.1 cc.) of pus was evacuated. The jugular vein was found thrombosed almost to the clavicle and was ligated as low as possible; the thrombus was removed from the vein and the sinus. The temperature gradually fell to normal, and the patient was discharged well.

CASE 19.—B. W., aged 19, who was eight months pregnant, had an acute tonsillitis six weeks before admission, with pain in the right ear one week later. The drum ruptured spontaneously several days later, but the pain persisted, and she had a chill three days before admission and another on the day before admission. She was admitted to the hospital on Oct. 22, 1913. The temperature was 98 F. A physical examination gave negative results. There was no discharge in the right auditory canal. There were a small perforation of the drum, tenderness of the right mastoid and slight injection of the tonsils and pharynx. A blood culture grew hemolytic streptococci. The mastoid, which was opened on Oct. 23, 1913, was found to be infected; a perisinuous abscess was located. The lateral sinus was incised, and the thrombus was removed. The internal jugular vein was ligated and divided. The patient had an uneventful recovery. The child was delivered on the third day after operation, but died within seven hours. It is interesting to note that hemolytic streptococci were isolated from the placental and fetal circulation.

CASE 20.—J. C., aged 15, had a cold in the head followed on Feb. 26, 1933, by pain in the right ear. The pain became more severe, and the drum was incised on March 2; there was a profuse pulsating discharge. Pain then developed in the region of the tip of the mastoid. The patient was admitted to the hospital on March 6. Physical examination gave negative results. There were a profuse pulsating discharge in the right auditory canal and tenderness of the right mastoid and sternocleidomastoid muscle. The white blood cells numbered 11,500. A blood culture grew 1 colony of the pneumococcus type III per cubic centimeter. The Wassermann reaction was 4+, and the patient was given antisyphilitic treatment. The mastoid was opened on March 11; the cells at the tip of the mastoid were infected, and an extensive perisinuous abscess was found. The wall of the sinus

was incised, the thrombus removed and the internal jugular vein ligated. The patient had an uneventful recovery.

CASE 21.—In N. C., aged 10 years, ten days before admission a sore throat and acute right otitis media developed with nausea, vomiting and prostration. The patient became much worse and two days before admission had chills, fever, delirium and a severe rigor. She was admitted to the hospital on May 28, 1925. The temperature was 104 F. The patient was extremely sick and had a discharge in the right ear. The white blood cells numbered 7,000. A blood culture showed hemolytic streptococci. The right mastoid was opened on June 1, but it was not infected. The lateral sinus was exposed and incised; an infected thrombus was removed and the jugular vein ligated. The patient had a succession of metastatic abscesses in spite of transfusions, and she became thin and emaciated. Blood cultures on July 20 grew hemolytic streptococci. The patient died.

Subgroup 3 is composed of 9 patients who had a simple mastoidectomy followed by jugular ligation a few days later (cases 22 to 30).

CASE 22.—L. D., aged 8 years, had pain and discharge from the left ear five days before admission and on the following day pain and discharge from the right ear. The pain was more severe and the discharge more profuse from the left ear. He was admitted to the hospital on June 10, 1931, quite sick, with discharging ears. The white blood cells numbered 19,400. A blood culture was sterile. Mastoidectomy on the left was performed on June 13; the mastoid was infected, and the sinus plate was necrotic. A perisinuous abscess was found; the wall of the sinus was thickened. The temperature fell to normal following the operation, but at midnight June 14 it rose to 105.4 F. The blood culture remained sterile, and on June 15 the left internal jugular vein was ligated. The temperature gradually became normal, and the patient made an uneventful recovery.

CASE 23.—J. L., aged 12 years, had a right earache on April 12, 1929, and the following day the temperature was 105 F.; the drum was incised, and a thin, watery discharge was obtained. On April 22 the temperature was 105 F.; the child became mildly delirious and had a chill, but on the next day the temperature was normal. The patient was admitted to the hospital on April 24. Examination gave negative results. The temperature was 102 F. The white blood cells numbered 18,000. The blood culture was sterile. A serous discharge was present in the right ear, but there was no definite evidence of mastoid involvement. On April 27, the child had a chill, and the next day the temperature suddenly rose to 104 F. and fell to normal. Mastoidectomy was done on April 29. The mastoid cells were extensively diseased, especially in the zygomatic region and in the sinodural angle, but the lateral sinus was not exposed. Following this operation, the temperature remained normal for two days, and the blood culture was sterile; then a septic temperature with chills developed. On May 5, a blood culture grew hemolytic streptococci. The right internal jugular vein was ligated, and the lateral sinus was exposed; a thrombus was found in the jugular bulb. Tenderness of the sternoclavicular joint developed, which subsided. Otherwise the convalescence was normal.

CASE 24.—R. T., aged 14 years, had measles three weeks before admission and two weeks later a pain in the right ear with rupture of the drum and a profuse discharge. The earache became worse, the discharge continued, and the day before admission he had pain in the left ear. He was admitted to the hospital on May 2, 1931. The temperature was 103.2 F. The right mastoid was acutely tender, and there was a profuse, pulsating, mucopurulent discharge in the right auditory canal. The left drum was red and bulged. The white blood cells numbered 16,600.

Mastoidectomy on the right was done on May 3, and all the cells were found to be infected. Pus welled up when the cortex was opened. The lateral sinus formed the floor of the mastoid and appeared to be normal. The temperature remained elevated. A blood culture on May 7 grew less than 1 colony of hemolytic streptococci per cubic centimeter. The mastoid was reopened, but the sinus was not thrombosed. On the following day, the patient had a chill, and the temperature was elevated. On May 9, the left mastoid was opened and found to be filled with pus and granulations; the left lateral sinus was normal. The right internal jugular vein was ligated. The temperature fell to normal but suddenly rose to 105.6 F. on May 12. The blood cultures on May 18 and 28 were sterile. Bronchopneumonia developed. Convalescence was long, but the patient finally recovered.

CASE 25.—J. S., aged 38, had an intermittent discharge from the right ear from childhood, and three months before admission a cold in the head and a more profuse and constant discharge from the right ear developed. The hearing in the right ear became progressively worse, and three days before admission pain developed in the region of the right mastoid and over the right side of the head. The patient was admitted to the hospital on April 2, 1917. The temperature was 100 F. General examination gave negative results. There were a purulent discharge in the right auditory canal and tenderness of the right mastoid. The white blood cells numbered 10,400. The mastoid was opened on April 3. A small perforation of the cortex which led to the lateral sinus was found; the cells were filled with thin pus, and the lateral sinus looked normal. The temperature fell to normal following the operation, but suddenly rose on April 8 to 103.6 F., and the blood culture grew 15 colonies of hemolytic streptococci per cubic centimeter. On April 9 the right internal jugular vein was ligated, and the lateral sinus was incised and bled freely. The blood culture on April 16 was sterile. A gluteal abscess developed which was incised and which on culture grew *Staphylococcus albus*. On April 24, a blood culture grew 2 colonies of nonhemolytic streptococci per cubic centimeter. The temperature fluctuated daily for two weeks. The patient was discharged well.

CASE 26.—E. H., aged 33, had a discharge and severe pain in the left ear of three months' duration, but no tinnitus or vertigo. She was admitted on Oct. 5, 1921. The temperature was 98 F. Physical examination gave negative results. There was a purulent discharge in the left ear, and the left drum was destroyed, with granulations in the middle ear. The white blood cells numbered 8,200. On October 6, the left mastoid was opened; the bone was densely hard, with no cells, and the antrum was filled with a cholesteatoma. The dura and the lateral sinus appeared to be normal. Following the operation the temperature remained normal, but on October 15 and 16 the patient had chills, with marked elevations of temperature. The white blood cells numbered 8,700. A blood culture grew nonhemolytic streptococci. Spinal puncture showed a clear fluid under normal pressure. The left internal jugular vein was ligated, and a thrombus was removed from the lateral sinus. The temperature remained elevated, and the patient became delirious with projectile vomiting. A lumbar puncture on October 19 showed 16 cells and another on October 20, 25 cells, and nonhemolytic streptococci were isolated on culture. The patient died.

CASE 27.—S. S., aged 14 years, had chronic otitis media on the right of one year's duration. Bilateral acute otitis media with a purulent discharge developed two weeks before admission. The child could not walk straight and was unable to see plainly on sitting up; the patient was forced to go to bed, and for two weeks

had constipation and vomiting. He was admitted on May 26, 1930, very sick, and with his face flushed. The temperature was 104.8 F. There was a thick, purulent discharge in the auditory canals, swelling and tenderness of the left mastoid and bilateral papilledema. The white cell count was 20,800. A blood culture was sterile. On May 28, he had a subtemporal decompression and received an injection of air. The fluid was found to be under pressure, but otherwise was normal. On May 30, mastoidectomy was done on the left side; all of the cells were filled with a thick mucoid discharge, and the sinus plate was necrotic, with a large exposure of the sinus and a perisinuous abscess. The temperature remained low, but suddenly rose to 105.4 F. on June 1; on the next day the left internal jugular vein was ligated; the lateral sinus was incised, and the thrombus was removed. The temperature fell to normal in a week; the blood culture was sterile, and the patient had an uneventful convalescence.

CASE 28.—L. L., aged 9 years, felt pain in the left ear on Feb. 8, 1924. The pain became progressively worse and the drum ruptured. The following week she was ill; the temperature was elevated irregularly, and there were loss of appetite and occasional vomiting. She became definitely more drowsy four days before admission; the temperature rose steadily and she was delirious at times. She was admitted on February 29. The temperature was 104 F. She was very ill, drowsy and weak. The left drum was injected and bulging; the mastoid was tender. There were bilateral choked disks and ankle clonus. The Kernig sign was positive on the right. A blood culture grew hemolytic streptococci, 70 colonies per cubic centimeter. A spinal puncture yielded a slightly turbid fluid under increased pressure and containing 750 cells. The white cells numbered 11,000. The left mastoid was opened on March 1, and a large area of the dura, which was more tense than normal, was exposed. The lateral sinus appeared to be normal. Lumbar puncture gave a cloudy fluid which contained 300 cells. The patient's condition remained unchanged. A blood culture on March 4 grew hemolytic streptococci, 15 colonies per cubic centimeter. The left internal jugular vein was ligated; the sinus, which was incised, bled freely. The temperature continued to fluctuate daily, and a blood culture on March 8 grew 60 colonies of hemolytic streptococci. The patient's condition grew progressively worse, and she died.

CASE 29.—O. E., aged 1 year, was seen in the dispensary on April 19, 1915, with bilateral otitis media. The drums were incised. The condition in the right ear subsided, but the left ear continued to discharge. The child was admitted on May 14. The temperature was 103 F. There was a mucopurulent discharge in the left auditory canal, with a swelling above and behind the left ear. The white blood cells numbered 17,000. A blood culture was sterile. Mastoidectomy was performed on May 15, and free pus was found in all of the cells; the bone was necrotic, but the lateral sinus appeared to be normal. The child's condition improved; the temperature gradually fell to normal, but on May 21 it suddenly rose to 105 F. The white cells numbered 12,000. A blood culture was sterile. On May 22 the left mastoid was reopened; the sinus was incised and bled freely. The temperature gradually fell until May 27, when it began to rise daily, with fluctuation. On June 6, the blood culture grew numerous colonies of streptococci, and on the following day the lateral sinus and internal jugular vein were exposed and found to be thrombosed from the torcular herophili to beyond the clavicle; the thrombus was removed as far as possible, and the vein was ligated. The patient recovered.

CASE 30.—D. T., aged 3 years, had chronic left otitis media, and was in a sanatorium for mediastinal tuberculosis. On Nov. 26, 1932, a pain in the left ear

with fever developed, and the patient did not eat well. She was admitted on November 27. The temperature was 103.2 F. There was a foul, serous discharge in the left auditory canal; the drum had been destroyed, and debris and granulations were present in the middle ear. There was tenderness of the left mastoid. The white blood cells numbered 31,600. The eyegrounds were normal. On November 28 a subperiosteal abscess was incised, and a foul, serous discharge was obtained. The temperature fell to normal, but rose to 105.4 F. on December 1. A blood culture was sterile. The left mastoid, which was opened on December 1, was found to be filled with foul, pulsating, dirty pus. A perforation of the cortex and a cholesteatoma in the antrum were found. The lateral sinus was entirely an abscess cavity. Blood cultures taken on December 2 and 3 were sterile, but others made on December 5 grew hemolytic streptococci. The temperature became elevated on December 5. The internal jugular vein was ligated, and the lateral sinus was cleaned until bleeding ensued. In spite of transfusions, pneumonia developed, and the patient died. Autopsy revealed infected infarcts and abscesses of the upper and lower lobes of both lungs and empyema of the left lung.

#### TREATMENT

In the treatment of lateral sinus thrombosis no hard and fast rule can be established to govern every case. Each patient requires individual study, and the aim of the surgeon should be to make the diagnosis as accurately as possible and to institute such surgical therapy as is indicated.

In the Johns Hopkins Hospital the surgical treatment of sinus thrombosis varies with the severity of the clinical symptoms. A simple mastoidectomy is performed on all of the patients. A radical operation is performed on the mastoid only if hearing is markedly impaired owing to an extensive suppuration of the middle ear or to cholesteatoma. If there is clinical evidence of septicemia, a portion of the lateral and sigmoid sinus is exposed for direct inspection, and as a rule, the sinus is opened, the clot removed, and the jugular vein ligated. In the absence of clinical evidence of septicemia it is advisable to establish drainage and to wait rather than to make an exploratory incision or puncture of the sinus through an infected field. In the great majority of our patients, however, the clinical symptoms and the subsequent course seem to justify early ligation of the jugular vein.

In 21 patients with proved sinus thrombosis only a simple mastoidectomy was performed at the first operation:

1. In 9 of these patients the continued septic temperature and other clinical evidences of a spreading infection necessitated a second operation at which the sinus was opened, the clot removed and the jugular vein ligated; of these 9 patients 6 recovered; the fatalities in 2 cases were due to meningitis and in 1 case (case 30, table) to multiple pulmonary abscesses. It is doubtful that an earlier ligation of the jugular vein would have prevented the meningitis.



# Summary of Thirty Cases of Sinus Thrombosis

Case	Age	Chills		Temperature Peak, F.	White Cell Count at Temperature Peak	Blood Culture Hem. str.*	Colonies per Cc. of Blood	Eyegrounds	Sphal. Puncture	Transfusions	Complications	Result
		Before	After									
1	46	Yes	Yes	105.2	9,800	Hem. str.*	25	Bilateral full veins	Not done	Two, 50 cc. each	Bronchopneumonia; thrombosis of right internal saphenous vein	Recovered
2	17	Yes	No	107.4	16,400	Latent sinus, Bacillus proteus	..	Bilateral full veins	Not done	None	None	Recovered
3	10	Yes	Yes	104.0	13,900	Hem. str.	..	Bilateral full veins	Not done	One, 250 cc.	None	Recovered
4	4	Yes	Yes	104.8	17,500	Hem. str.	20	Not examined	Not done	Four, 350 to 250 cc. each	Redness and swelling of right ankle; abscess of right hip	Recovered
5	3	No	No	105.0	13,200	No growth	..	Bilateral choked disks	Not done	Two, 175 cc. each	Abscess of right elbow and left hip	Recovered
6	4	No	No	105.6	18,200	Hem. str.	6,000	Bilateral choked disks	Normal	Two, 250 cc. each	Bronchopneumonia	Died
7	2½	No	No	105.0	21,000	Hem. str.	..	Bilateral full veins	Turbid fluid which grew streptococci	One, 100 cc.	Abscess of left hip; meningitis	Died
8	18	Yes	No	106.0	5,800	No growth	..	Normal	Not done	Six, 250 cc. each	None	Recovered
9	7	No	No	100.0	14,000	No growth	..	Normal	Not done	None	None	Recovered
10	25	No	No	105.0	.....	Hem. str.	25	Normal	Normal	None	Multiple pulmonary abscesses	Died
11	3	No	No	103.8	17,200	No growth	..	Not examined	Not done	None	None	Recovered
12	54	No	No	105.0	8,200	None	..	Right choked disk	Negative	None	Necrosis of right temporal bone	Died
13	64	No	No	99.0	10,200	None	..	Bilateral papilledema	Negative	None	Cerebellar abscess	Died
14	6	Yes	No	104.6	19,200	No growth	..	Bilateral choked disks	Pressure increased	None	None	Recovered
15	4	No	No	106.8	31,200	No growth	..	Normal	Not done	Two, 200 cc. each	None	Recovered
16	54	Yes	No	106.0	12,600	Nonhem. str.	10	Normal	Pressure increased	None	None	Recovered

17	40	Yes	No	103.0	15,000	Item. str.	1	Bilateral papilledema Not exam- ined	Normal 20 cells	One, 450 cc.	Ptosis of right upper eyelid None	Recovered
18	7	Yes	No	103.6	20,200	No growth	..	Veins full on right	Not done	None	None	Recovered
19	19	Yes	No	101.0	11,200	Item. str.	..	Right disk blurred on nasal side	Not done	None	None	Recovered
20	18	No	No	103.0	11,400	Pneumococcus type III	1	Both disks blurred on nasal side	Not done	Four, 275 cc. each	Abscess of the left arm, left ear, parotids, lips and body	Died
21	10	Rigor	No	100.0	7,000	Item. str.	..	Less on right Not exam- ined	Not done	Two, 175 cc. each	Pain and redness of right knee	Recovered
22	8	Yes	No	105.6	19,400	No growth	..	Normal	Not done	One, 200 cc.	Pain in right shoulder; redness and tenderness of sternoclavicular joint	Recovered
23	12	Yes	Yes	104.0	18,000	Item. str.	..	Normal	Not done	Two, 250 cc. each	Pain and redness of sternoclavicular joint	Recovered
24	14	Yes	No	105.0	16,200	Item. str.	..	Normal	Not done	None	Glutic abscess	Died
25	33	No	No	103.8	12,600	Item. str.	15	Nasal mar- gins of both disks blurred	25 cells; nonhemolytic streptococci	None	Meningitis	Recovered
26	31	Yes	No	104.8	8,700	Nonhem. str.	..	Bilateral papilledema	Increased pressure	None	None	Died
27	14	No	No	105.2	15,000	No growth	..	Bilateral papilledema	Increased pressure; turbid fluid, 750 cells	None	None	Recovered
28	9	No	No	106.5	11,000	Item. str.	60	Normal	Not done	None	Abscess of leg	Died
29	1	No	No	100.0	16,000	Item. str.	..	Bilateral hazy disks	Not done	Three, 125 cc. each	Multiple pulmonary abscess	Died
30	3	No	No	105.4	27,000	Item. str.	..					

\* Hemolytic streptococci.

2. In 6 of the patients the sinus was not opened, and the vein was not ligated; 3 patients recovered (50 per cent). The fatalities were due to multiple pulmonary abscesses (case 10), suppurative labyrinthitis (case 12) and a cerebellar abscess with terminal pneumonia (case 13).

3. Six patients had a simple operation on the mastoid before admission to this hospital. At a later date, varying from six to twenty-three days after the operation on the mastoid the sinus was opened, the thrombus removed and the jugular vein ligated; 3 patients (50 per cent) recovered. The fatalities were due to an overwhelming septicemia (6,000 colonies of hemolytic streptococci per cubic centimeter, case 6), pyemia with marked secondary anemia (case 5) and suppurative meningitis (case 7).

In 8 of the remaining 9 patients the mastoid was opened, the sinus incised, the clot removed and the internal jugular vein ligated at one operation. In 1 of these patients (case 2) the jugular vein was not ligated. The patient recovered. There was only 1 fatality in this group of 9 patients (case 21). Therefore 8 patients (89 per cent) in the group recovered.

#### PATHOLOGY AND ETIOLOGY

The hemolytic streptococcus is reported as the organism most commonly isolated in otitic sinus thrombosis. In our series this organism was grown from the blood in 15 patients, but from the mastoid wound in only 5; the nonhemolytic streptococcus was grown from both the blood and the mastoid in 2 patients; the pneumococcus type III was grown from the mastoid in 2 patients and from the blood in only 1. No patient in this series had staphylococcic septicemia.

A perisinous abscess was found in 14 of our 30 cases (47 per cent) in association with erosion of the bone overlying the sinus. In 3 patients thrombosis of the lateral sinus was found at autopsy, but its presence could not be demonstrated at operation. Acute otitis media was the first symptom in 21 patients, and in 9 patients there was an acute flare-up of chronic otitis media.

Sections made from a portion of the sinus wall excised at operation showed an acute inflammatory process and at times an infiltration with red blood cells. It is our impression that the progression of the thrombus is due primarily to the extension of the inflammatory process in the wall of the sinus or vein and not to an extension of the infection in the thrombus.

#### SUMMARY

1. Thirty patients with lateral sinus thrombosis are presented in this paper, 16 of whom were children under 14 years of age. Sinus thrombosis occurs in infancy (case 29) as well as in old age (case 13).

2. The syndrome of chills, a septic temperature and a positive blood culture are often absent. In this series 15 (50 per cent) of the patients had chills; 20 (66 per cent) of the patients had a septic temperature, and in only 9 (30 per cent) of the patients was a positive blood culture obtained before operation. Only 6 patients (20 per cent) had the combination of chills, a septic temperature and a positive blood culture before operation.

3. The white cell count, the temperature and the result of blood culture are shown in the table. A white cell count of 5,800 was associated with a temperature of 106 F. (case 8); a count of 8,700 with a temperature of 104.8 F., a positive blood culture and meningitis (case 26) and a count of 9,800 with a temperature of 105.2 and 26 colonies of hemolytic streptococci in the blood of a woman, aged 46 who recovered (case 1). As a rule, the blood count is higher in children than in adults.

4. The hemolytic streptococcus is the organism most commonly found in the blood in cases of otitic sinus thrombosis (50 per cent of our series). A culture from the mastoid or middle ear may give no indication of the organism in the blood stream, because the staphylococcus or other organisms frequently present in this location overgrow and prevent the recognition of the hemolytic streptococcus.

5. Following operation the temperature may remain elevated for as long as a week, but in uncomplicated cases the general direction of the curve is toward normal. A secondary abscess and pneumonia are the common causes of a continued septic temperature.

6. Chills were noted as a symptom in 15 patients. In 4 of these patients the chills continued for several days after the operation, which consisted of a simple mastoidectomy, incision of the sinus, removal of the thrombus and ligation of the jugular vein. In 3 of the 4 patients the continuation of the chills was probably due to a complication: pneumonia (case 1), abscess of the hip (case 4) and involvement of the sternoclavicular joint (case 23). In 1 patient, however, there were no complications to explain the continuation of the chills for four days (case 3).

7. Transfusions were used as a therapeutic measure in 14 patients. It is our impression that they are of decided value, provided the cross-matching is carefully done and the blood is given slowly enough to prevent severe systemic reactions. The number of patients who were given transfusions, the number of transfusions given and the more important clinical findings are shown in the table.

8. Ten patients in this series of 30 cases died, a mortality of 33 per cent; of the 20 patients (66 per cent) who recovered, 3 (15 per cent) had pain, redness and swelling around one or more of the joints, 2 (10 per cent) had isolated abscesses of the muscles of the leg, and 2 (10 per cent) had pneumonia. The complications are shown in the table.

## VESICAL DISTENTION

### II. EFFECTS ON THE MOTOR MECHANISM OF THE UPPER URINARY TRACT; AN EXPERIMENTAL STUDY

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MINNEAPOLIS

The effects of distention of the urinary bladder on both the bladder itself and on the upper urinary tract have been studied and reported frequently in the past. Unfortunately, each investigator concerned himself with some isolated aspect of the problem, so that a coherent report of the process as a whole remains to be presented. For example, the changes which urethral ligature produces in the bladder, ureters and kidneys are well known. The mechanism by which these changes are produced has, however, remained relatively uncertain. Again, the question of the reflux of bladder urine into the ureters has been almost exhausted both experimentally and clinically; whether this phenomenon occurs in acute retention has been but little investigated. Also, research on the effects of rapid artificial filling of the bladder has led to results diametrically opposed, so far as the behavior of the kidneys and ureters is concerned.

It is the purpose of this article to present, in an orderly manner, the effects of urinary retention and of rapid artificial filling of the urinary bladder on the motor activity of the bladder and the ureters and to interpret their clinical significance. With this end in view, urinary retention was produced in the dog, and its effect on ureteral activity was studied. The function of the ureter during rapid artificial filling of the bladder was investigated, and a reflex, apparently not hitherto described, was discovered. This reflex evidently acts as an important mechanism, comparable to that which prevents urinary reflux, in protecting the upper urinary tract against sudden rises in intravesical tension.

#### REVIEW OF THE LITERATURE

The first phases of vesical distention to be well studied were the anatomic changes resulting from urethral ligature. Guyon and Albarran<sup>1</sup>

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Abridgment of a portion of a thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Guyon, J. F., and Albarran, J.: *Anatomie et physiologie de la rétention d'urine*. Arch. de méd. expér. et d'anat. 2:181, 1890.

obstructed the urethra of the dog and rabbit and observed the animals for periods up to seventy-two hours. They found that the chief anatomic changes consisted of hemorrhages, which appeared earliest in the vesical submucosa, spread later through the whole thickness of the wall of the bladder, and finally developed in the pelvis and parenchyma of the kidney. After from sixty to seventy-two hours the hemorrhages in the wall of the bladder led to necrosis, rupture and urinary peritonitis.

The occurrence of these changes was verified by the subsequent studies of Shigematsu<sup>2</sup> and of myself.

Guyon and Albarran stated that peristalsis disappeared from the ureter within twenty-four hours, while irritability to galvanism vanished within thirty-six hours. While Shigematsu's findings agreed with those of Guyon and Albarran, I have observed peristalsis even after seventy-two hours.

Guyon and Albarran observed progressive diminution in the urea content of the urine in each successive twenty-four hour period after obstruction had been established.

These are the only experimental studies which I have found which bear on the effects of urinary retention. For corroboration of these findings, one must review the literature of ureteral obstruction.

Cohnheim,<sup>3</sup> Lindemann,<sup>4</sup> Lucas,<sup>5</sup> Newman<sup>6</sup> and Winton<sup>7</sup> found that the flow of blood from the renal vein is diminished by distention of the renal pelvis. Fabian,<sup>8</sup> Corbett<sup>9</sup> and Helmholz and Field<sup>10</sup> ligated the ureters of the guinea-pig, dog and rabbit, respectively, and found that hemorrhages in the pelvic wall and renal parenchyma resulted. These observations may be combined to show that the retention of urine,

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2. Shigematsu, H.: Etude expérimentelle de la rétention d'urine, *J. d'urol.* **25:16**, 1928.

3. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.

4. Lindemann, W.: Ueber die Wirkung der Gegendruckerhöhung auf die Harnsekretion, *Beitr. z. path. Anat. u. z. allg. Path.* **21:500**, 1897.

5. Lucas, D. R.: On the Intraureteral Pressure and Its Relation to the Peristaltic Movements of the Ureter, *Proc. Soc. Exper. Biol. & Med.* **2:61**, 1904; Studies of the Peristalsis of the Ureter in Dogs by the Graphic Method, *Am. J. Physiol.* **17:392**, 1906-1907.

6. Newman, D.: Residual Urine and the Senile Bladder, *Glasgow M. J.* **87:73**, 1917.

7. Winton, F. R.: Influence of Increase of Ureter Pressure on the Isolated Mammalian Kidney, *J. Physiol.* **71:381**, 1931.

8. Fabian, E.: Die Niere des Kaninchens nach der Unterbindung ihres Harnleiters, *Biblioth. med. Abt. Path. u. path. Anat.* 1904, pt. 18, p. 1.

9. Corbett, J. F.: Changes in the Kidney Resulting from Tying the Ureter, *Am. J. M. Sc.* **141:568**, 1912.

10. Helmholz, H. F., and Field, R. S.: Acute Changes in the Rabbit's Kidney, Particularly the Pelvis, Produced by Ligating the Ureter, *J. Urol.* **15:409**, 1926.

whether in the bladder or in the pelvis of the kidney, interferes seriously with the blood supply of the urinary tract. That this is the case as concerns the kidney was demonstrated conclusively by Hinman and his co-workers.<sup>11</sup> They showed, chiefly by corrosion specimens, that a remarkable diminution in the size and number of the blood vessels of the kidney follows ureteral occlusion.

How are these changes produced? In order to answer this question it is desirable first to scrutinize the ability of the kidney and ureter, as well as of the bladder, to generate pressure.

It is difficult to establish the normal pressure relations in the urinary tract. Lucas,<sup>5</sup> from studies of the anesthetized dog (morphine), believed that the tension in the pelvis was usually negative, while that in the vesical end of the ureter might reach a few centimeters of water; he found that the excised ureter of a normal dog could exert a distending pressure of 92 cm. of water.

Beresnegowsky<sup>12</sup> observed individual peristaltic waves as high as 21 mm. of mercury in a woman with a ureterovaginal fistula. This cannot be regarded as normal, however, since such fistulas are usually associated with some fibrosis and hypertrophy of the ureter. Henderson<sup>13</sup> observed individual waves of 36 mm. in the dog.

Trattner<sup>14</sup> found that the pressure in the normal human ureter (ureteral catheter) ranged from 2 to 10 cm. of water.

The maximum pressure which may be generated by the normal kidney and ureter together has been thoroughly studied by allowing them to act against a rising vertical column of urine in a glass tube. The resultant tension has varied from a minimum of 40 or 50 mm. of mercury in the anesthetized dog (Heidenhain<sup>15</sup>) to a maximum of 76

11. Hinman, F., and Morrison, D. M.: Experimental Hydronephrosis, *J. Urol.* **11**:435, 1924. Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development; Partial Obstruction of Renal Artery; Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, *Arch. Surg.* **11**:649 (Nov.) 1925; Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development, and Significance of Venous Collateral System; Partial Obstruction of Renal Vein Without and With Ligation of All Collateral Veins, *ibid.* **11**:917 (Dec.) 1925; Experimental Hydronephrosis; Effect of Ligation of One Branch of Renal Artery on Its Rate of Development; Simultaneous Ligation of Posterior Branch of Renal Artery and Ureter on Same Side, *ibid.* **12**:830 (April) 1926.

12. Beresnegowsky, N.: Zur Frage ueber die physiologische Tätigkeit der Ureteren, *Zentralbl. f. Physiol.* **22**:461, 1908.

13. Henderson, V. E.: The Factors of the Ureter Pressure, *J. Physiol.* **33**:175, 1905.

14. Trattner, H. R.: Ureteral Activity in Some Pathologic Conditions Studied by Graphic Manometric Method, *Arch. Surg.* **17**:968 (Dec.) 1928.

15. Heidenhain, R.: Die Harnabsonderung, in Hermann, L.: *Handbuch der Physiologie*, Leipzig, F. C. W. Vogel, 1881, vol. 5, pt. 1, p. 299.



mm. in the anesthetized rabbit during caffeine diureses (Gottlieb and Magnus<sup>16</sup>). Beresnegowsky<sup>12</sup> observed a tension of 70 mm. in an unanesthetized human female with a ureterovaginal fistula. Kreutzmann<sup>17</sup> found a maximum pressure of 66 mm. of mercury in the ureter during straining, making his measurements by means of a ureteral catheter passed through a cystoscope.

These studies refer only to pressures exerted by the normal pelvis and ureter. I have been unable to find data on those attainable with hypertrophied organs.

More information is available as to the potentialities of the bladder. Dubois<sup>18</sup> and Adler<sup>19</sup> found pressures of from 6 to 12 cm. of water (from 4.4 to 8.8 mm. of mercury) in the resting bladder. Estimates of the level which provokes the desire to void vary from 10 cm. of water (7.3 mm. of mercury)—Hirsch<sup>20</sup>—to 29.9 cm. of water (22 mm. of mercury)—Kreutzmann.<sup>17</sup> During micturition the tension averages 78 cm. of water (57.3 mm. of mercury), but may reach 86 cm. (63.2 mm.)—Schwarz and Brenner.<sup>21</sup>

Estimates of the maximum tension attainable by the normal bladder vary widely from 80 cm. of water (58.8 mm. of mercury)—Rose<sup>22</sup>—to 133 cm. of water (97.8 mm. of mercury)—Kreutzmann.<sup>17</sup>

One can gain from the literature only a vague idea as to the influence of obstruction of the vesical neck with its presumed hypertrophy of the wall of the bladder on the contractile power of the bladder. Many have recorded the intravesical tension during chronic and acute retention from this cause, but have neglected to make it plain whether, in a given case, the wall of the bladder was the seat of hypertrophy or atrophy. Many urologists claim to have seen the urine "shoot clear to the ceiling" when an obstructed bladder was opened or catheterized, but actual measurements in such circumstances have shown the pressure to range from 9 or 10 (Dubois<sup>18</sup>) to 50 cm. of water (Bumpus and

16. Gottlieb, R., and Magnus, R.: Ueber Diurese, Arch. f. exper. Path. u. Pharmacol. **45**:223, 1901.

17. Kreutzmann, H. A. R.: Studies in Normal Ureteral and Vesical Pressure, J. Urol. **19**:517, 1928.

18. Dubois, P.: Ueber den Druck in der Harnblase, Deutsches Arch. f. klin. Med. **17**:148, 1876.

19. Adler, A.: Ueber den Druck in der Harnblase zugleich ein Beitrag zur Funktion des Blasenmechanismus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **30**:487, 1918.

20. Hirsch, E. W.: Relation of Bladder Pressure to Bladder Function, J. A. M. A. **91**:772 (Sept. 15) 1928.

21. Schwarz, O., and Brenner, A.: Untersuchungen ueber die Physiologie und Pathologie der Blasenfunktion, Ztschr. f. urol. Chir. **8**:32, 1921.

22. Rose, D. K.: Clinical Application of Bladder Physiology, J. Urol. **26**:91, 1931.

Foulds<sup>23</sup>). Intermediate values are: 28.5 cm. (Campbell,<sup>24</sup> average of 11 cases) and from 26 to 39 cm. (Pilcher<sup>25</sup>).

From these data it is clear that either the upper or the lower portion of the urinary tract can easily generate a pressure sufficiently high to interfere seriously with its own venous, and at times arterial, circulation.

Starling<sup>26</sup> stated that the pressure in the radial artery (comparable in size to the vesical artery) averages 85 mm. of mercury (114 cm. of water); the venous tension in vessels of comparable size is 9 mm. of mercury (12 cm. of water) or less. The danger of even moderate rises in pressure within the bladder, especially if prolonged, is therefore obvious.

Various means have been used to study the effect of rapid artificial filling of the bladder on both its own activity and that of the upper urinary tract.

The most striking feature of the response of the bladder to distention is its tendency to maintain, within wide limits of filling, a constant pressure, a fact which has been emphasized by Mosso and Pellacani,<sup>27</sup> Sherrington,<sup>28</sup> Rose<sup>22</sup> and others. The level of this pressure appears to be rather constant, but varies with certain extraneous influences (Mosso and Pellacani,<sup>26</sup> Hirsch<sup>20</sup> and Boeminghaus<sup>29</sup>), such as temperature and psychic stimuli. It ranges between 6 and 12 cm. of water. When distention is carried past the capacity of the bladder to relax, very high pressures may result. Goltz<sup>30</sup> observed rhythmic contractions of the wall of the bladder during filling. Rose<sup>22</sup> and others noted that once the bladder has been filled and emptied immediate refilling with a similar quantity of fluid provokes a sharper reaction than does the first injection.

Hitherto it has generally been believed that high pressures in the bladder develop as a consequence of the muscular activity of its own

23. Bumpus, H. C., Jr., and Foulds, G. S.: Gradual Emptying of the Over-distended Bladder, *J. A. M. A.* **81**:821 (Sept. 8) 1923.

24. Campbell, M. F.: Studies in Bladder Decompression, *J. Urol.* **17**:371, 1927.

25. Pilcher, P. M.: Prostatectomy in Two Stages, *Ann. Surg.* **59**:500, 1914.

26. Starling, E. H.: Principles of Physiology, ed. 5, Philadelphia, Lea & Febiger, 1930, p. 763.

27. Mosso, A., and Pellacani, P.: Sur les fonctions de la vessie, *Arch. ital. de biol.* **1**:97 and 291, 1882.

28. Sherrington, C. S.: Postural Activity of Muscle and Nerve: II. Visceral Muscle, *Brain* **38**:213, 1915.

29. Boeminghaus, H.: Zur Feststellung des Einflusses der Blasenfüllung auf die Funktion der Nieren, *Deutsche med. Wchnschr.* **51**:138, 1925; Ueber funktionelle Zusammenhänge zwischen Harnblase und Niere (vesico-renaler Reflex), *Arch. f. klin. Chir.* **154**:114, 1929.

30. Goltz, F.: Ueber die Funktionen des Lendenmarks des Hundes, *Arch. f. d. ges. Physiol.* **8**:460, 1874.

wall. However, as I have shown, the detrusor urinae of the dog is normally incapable of exerting pressures of more than 30 to 40 cm. of water (from 22 to 29 mm. of mercury) on stimulation, and pressures above this level result from contraction of the abdominal wall and the diaphragm, i. e., attempts to void. True, high pressures can be produced in the exposed bladder, which is thus free from the influence of voluntary muscular contraction, but in this case they represent not the activity of the bladder but an external force (the pressure of the fluid injected) exerted against the wall of a bladder distended to such a degree that it can relax no further.

When distention sufficient to raise the intravesical pressure is employed, ureteral peristalsis is altered. Sampson<sup>31</sup> studied the excised fresh urinary tract of the dog and found that filling the bladder caused an increase in the frequency and a diminution in the amplitude of the peristaltic waves.

Lucas<sup>5</sup> traced ureteral peristalsis in the dog under morphine by means of a T-cannula and kymograph; an increase in intravesical tension caused also a quickening of ureteral peristalsis with a diminution in its amplitude. Israel<sup>32</sup> obtained similar results in etherized dogs. Pico<sup>33</sup> and Sérès<sup>34</sup> observed peristalsis in the exposed ureter and measured the outflow from its cut proximal end during distention of the bladder; they found it increased in the anesthetized dog. Graves and Davidoff<sup>35</sup> and Wislocki and O'Connor<sup>36</sup> found peristalsis in the exposed ureter of the anesthetized rabbit increased by vesical distention.

Pflaumer<sup>37</sup> watched with the cystoscope the jets of urine which escaped from the ureteral meatus of the unanesthetized dog and found

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31. Sampson, J. A.: Ascending Renal Infection with Especial Reference to the Reflux of Urine from the Bladder into the Ureters, *Bull. Johns Hopkins Hosp.* **14**:334, 1903.

32. Israel, W.: Das Verhalten der Nieren- und Harnleiter-Tätigkeit während der Blasenkontraktion, *Ztschr. f. Urol.* **21**:614, 1924; Harnleitermündung und Blasenkontraktion, *Klin. Wchnschr.* **5**:1878, 1926.

33. Pico, O. M.: Réflexe vesico-rénal, *Compt. rend. Soc. de biol.* **83**:1499, 1920.

34. Sérès, M.: Corrélation fonctionnelle vésicorénale, *J. d'urol.* **16**:177, 1923.

35. Graves, R. C., and Davidoff, L. M.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, *J. Urol.* **10**:185, 1923; Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, *ibid.* **12**:93, 1924; Studies on the Ureter and Bladder with Especial Reference to Regurgitation of Vesical Contents; Regurgitation as Observed in Cats and Dogs, *ibid.* **14**:1, 1925. Graves, R. C.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents: Bladder Pressure-Curve in the Human, *ibid.* **18**:321, 1927.

36. Wislocki, G. B., and O'Connor, V. J.: Experimental Observations upon the Ureters, with Especial Reference to Peristalsis and Antiperistalsis, *Bull. Johns Hopkins Hosp.* **31**:197, 1920.

37. Pflaumer, E.: Cystoskopische Beobachtungen zur Physiologie der Harnleiter und Nieren, *Ztschr. f. Urol.* **13**:367, 1919. Pflaumer, E., and Höcker, H.: Ureterphysiologie und Uroselectan, *Deutsche Ztschr. f. Chir.* **229**:309, 1930.

that increased intravesical pressure led to a diminution in their frequency and volume, an observation which was verified by Schmidt<sup>38</sup> in man. These investigators attributed the change to compression of the intramural ureter.

Kreutzmann,<sup>17</sup> using a catheter passed through the cystoscope, found that a rise in the pressure in the bladder increased tension in the ureter in man, but did not exclude the possibility of regurgitation of the contents of the bladder alongside the catheter.

A perusal of what has been written about the possibility of regurgitation of the bladder urine into the ureters during vesical distention is apt to be confusing. Semblinow,<sup>39</sup> Lewin and Goldschmidt,<sup>40</sup> Courtade and Guyon,<sup>41</sup> Markus,<sup>42</sup> Wislocki and O'Connor,<sup>36</sup> von Lichtenberg<sup>43</sup> and Graves and Davidoff<sup>35</sup> all observed such regurgitation into the ureter of the anesthetized rabbit. On the other hand, Sampson,<sup>21</sup> Lucas,<sup>5</sup> Draper and Braasch<sup>44</sup> and Bush and McCradie<sup>45</sup> were unable to produce it in the dog. Satani<sup>46</sup> denied its occurrence in the pig. Eisendrath,<sup>47</sup> Schmidt,<sup>38</sup> Kelly,<sup>48</sup> Young,<sup>49</sup> Bumpus<sup>49a</sup> and others do not believe

38. Schmidt, A.: Die Insufficienz der vesikalen Harnleitermündung und der Funktionszustand der Harnleitermuskulatur, *Beitr. z. klin. Chir.* **141**:50, 1927.

39. Semblinow: Zur Pathologie der durch Bakterien bewirkten aufsteigenden Nephritis, *Inaug. Dissert.*, 1885.

40. Lewin, L., and Goldschmidt, H.: Die Resorption körperfremder Stoffe aus der Harnblase, *Arch. f. exper. Path. u. Pharmacol.* **37**:60, 1896.

41. Courtade, D., and Guyon, J. F.: Sur le reflux du contenu vésical dans les urèteres, *Compt. rend. Soc. de biol.* **46**:556, 1894.

42. Markus, H.: Experimentelle Untersuchung ueber das Rückströmen von Blaseninhalt, *Wien. klin. Wchnschr.* **16**:725, 1908.

43. von Lichtenberg, A.: Ueber den Begriff "Hydronephrose" in allgemeinen und ueber den Nachweis der durch akzessorische Gefäße verursachten "Hydronephrose" mit der Roentgenuntersuchung, *Ztschr. f. Urol.* **18**:585, 1924.

44. Draper, J. W., and Braasch, W. F.: The Function of the Ureterovesical Valve, *J. A. M. A.* **60**:20 (Jan. 4) 1913.

45. Bush, A. D., and McCradie, R. S.: Competency of the Ureterovesical Valves, *Am. J. Physiol.* **68**:107, 1924.

46. Satani, Y.: Experimental Studies on the Ureter, *Am. J. Physiol.* **49**:474, 1919; *ibid.* **50**:342, 1919.

47. Eisendrath, D. N.; Katz, H., and Glasser, J. M.: Bladder Reflux; Clinical and Experimental Study, *J. A. M. A.* **85**:1121 (Oct. 10) 1925.

48. Kelly, H. A.: The Reflux of Air into the Ureters Through the Air-Distended Bladder in the Knee-Breast Posture, *Am. J. Obst.* **40**:468, 1879.

49. Young, H. H.: Hydraulic Pressure in Genitourinary Practice, Especially in Contracture of the Bladder, *Bull. Johns Hopkins Hosp.* **9**:100, 1898; *Practice of Urology*, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 17.

49a. Bumpus, H. C.: Urinary Reflux, *J. Urol.* **12**:341, 1924.

that it occurs normally in man, while Kretschmer<sup>50</sup> and Graves<sup>51</sup> observed it (contrast medium under the fluoroscope) in apparently normal persons.

Sampson's<sup>51</sup> original description of the ureterovesical valve did much to clarify the situation, but the most adequate explanation of the confusion is that of Gruber,<sup>52</sup> who pointed out that the ureter of the dog and pig and of man enters the bladder obliquely and is guarded by a thick, well developed valve, while that of the rabbit passes through the wall of the bladder almost at right angles and possesses little or nothing in the way of a valve. He was able to produce reflux in the dog only after injuring the valve. De la Pena<sup>53</sup> obtained similar results from dividing the fibers of the detrusor urinae from without in the area where they overlie the intramural ureter, thus affirming the importance of both the valve and the oblique course of the ureter in preventing reflux. The clinical importance of these factors has been emphasized by Young,<sup>49</sup> Kelly,<sup>48</sup> Warschauer,<sup>54</sup> Alksne,<sup>55</sup> Eisendrath,<sup>47</sup> Satani,<sup>46</sup> Bumpus, Caulk<sup>56</sup> and others.

To summarize, during filling of the bladder, high pressures may develop. When these pressures exceed from 30 to 40 cm. of water, the excess is apparently due either to distention of the organ to such a degree that it can no longer relax or to contraction of the abdominal muscles and the diaphragm. When the intravesical tension rises above 6 to 12 cm. of water, the rate of ureteral peristalsis is increased, while its amplitude is diminished. In spite of the increased rate of peristalsis in the ureter, the frequency with which jets of urine are ejected into the bladder is diminished. This seeming discrepancy is probably to be explained by the fact that most observers have selected one area in the ureter for observation and have not considered the fact that the rate in the vesical end of the ureter is normally lower than that elsewhere (Boulet<sup>57</sup>).

50. Kretschmer, H. L.: Cystography, Surg., Gynec. & Obst. **23**:709, 1916.

51. Graves, R. C.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, Tr. Am. A. Genito-Urin. Surgeons **20**: 98, 1927.

52. Gruber, C. M.: The Function of the Ureterovesical Valve and the Experimental Production of Hydronephrosis, J. Urol. **23**:161, 1930.

53. de la Pena, A.: Personal communication to the author.

54. Warschauer, E.: Beobachtungen aus der Nieren- und Ureteren- Physiologie, Berl. klin. Wchnschr. **38**:398, 1901.

55. Alksne, J.: Ein Beitrag zur normalen und pathologischen Physiologie des Ureters, Folia urol. **1**:338, 1907-1908.

56. Caulk, J. R.: The Significance of the Ureter in Surgery, Surg., Gynec. & Obst. **49**:228, 1929.

57. Boulet, L.: Sur les mouvements de l'urètre humain, Compt. rend. Soc. de biol. **74**:1171, 1913.

Reflux probably does not occur in the ureters of the normal human being or dog because of their oblique course, which leads to compression by the contents of the bladder, and because of the valves which guard them. Exceptions like those of Kretschmer<sup>50</sup> and Graves<sup>51</sup> are best explained by the fact that the ordinary contrast mediums cause sufficient irritation to set up abnormal conditions, so that the regurgitation of such solutions up the ureters or normal human beings is not a "normal" phenomenon (Schmidt<sup>55</sup>).

#### EXPERIMENTAL STUDY

Normal male dogs were used. Anesthesia was obtained by the subcutaneous injection of 10 mg. of morphine sulphate for each kilogram of body weight, supplemented, if necessary, by infiltration of the abdominal wall with 0.5 per cent procaine hydrochloride without epinephrine hydrochloride. Through an incision in the left rectus abdominis the left ureter was exposed just above the point at which it crossed the iliac vessels. It was not stripped, but the muscularis was

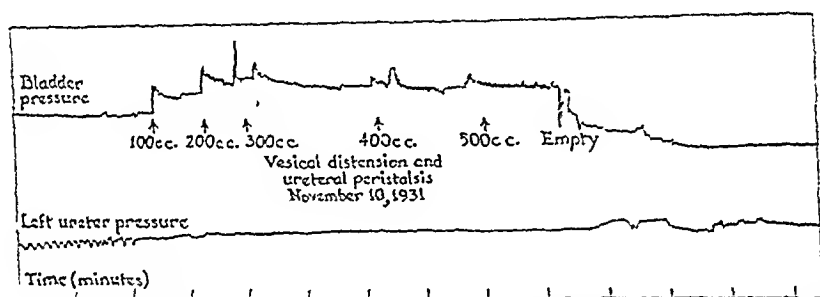


Fig. 1 (experiment 1).—Kymograph tracing showing cessation of ureteral peristalsis on distention of the bladder; peristalsis returned on emptying it.

transfixed by a fine silk traction suture. A short longitudinal incision was made into its lumen just below the suture, and a T-cannula made from a 20 gage steel needle was inserted. The ureteral incision was closed with silk sutures snugly enough to be water-tight. The cannula was connected to a glass tube, which was brought out through a stab wound in the lateral abdominal wall. The tube was stitched to the posterior abdominal wall to prevent kinking of the ureter. The right ureter was divided near the bladder, and the vesical end was cannulated. The renal end was left open. The cannula was connected to a rubber tube which was brought out through the abdominal incision and allowed to drain into a cup.

The glass tube from the left ureter was then connected to a water manometer which recorded on smoked paper in a kymograph. A rubber catheter was passed into the bladder and connected, by means of a T-tube and a three-way valve, to a reservoir of sterile physiologic solution of sodium chloride, colored blue with indigotindisulphonate, U.S.P. (indigocarmine), and kept at body temperature, and to a mercury manometer which also recorded on the smoked paper.

When peristaltic waves appeared, the bladder was distended by injecting 50 cc. of colored sterile saline solution, and the resultant pressure in the bladder and ureter was recorded.

EXPERIMENT 1.—In a male dog weighing 12 Kg. peristaltic waves appeared directly the apparatus was set up. When 100 cc. of fluid had been injected into

the bladder, the waves suddenly disappeared (fig. 1). This occurred with an intravesical pressure of 22 mm. of mercury (30 cm. of water). Injection was continued until the bladder contained 500 cc. at a pressure of 100 mm. of mercury. Emptying of the bladder was followed by a return of peristalsis and by a sharp rise of tension. The frequency of peristalsis was increased, but its amplitude was diminished. At no time did indigotindisulphonate appear in the glass tube leading from the left ureter or from the distal stump of the right ureter.

EXPERIMENT 2.—In a male dog weighing 15 Kg. the procedure was carried out as in the foregoing experiment, except that the injections were made in quantities of 100 cc. Peristalsis disappeared at a vesical tension of 26 mm. of mercury. When 500 cc. had been injected (pressure, 122 mm.) the bladder unexpectedly burst (fig. 2). There was a sharp rise of intra-ureteral tension within a few seconds, accompanied by small frequent peristaltic waves. No indigotindisulphonate appeared in the glass tube connected to the ureteral cannula or from the vesical end of the right ureter.

EXPERIMENTS 3 and 4.—These were identical with experiment 1. Peristalsis disappeared when the intravesical tension exceeded 31 mm. of mercury (42 cm. of

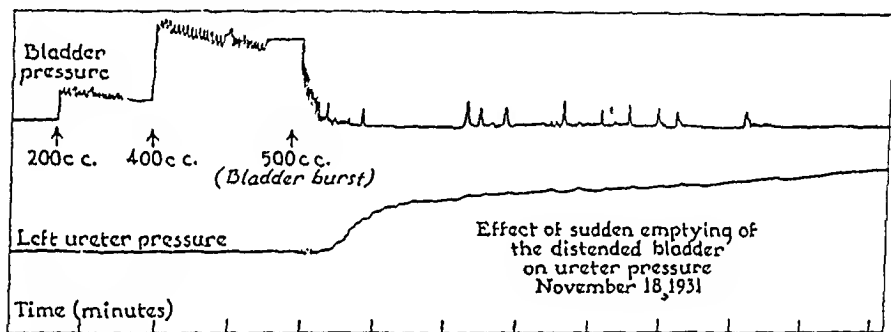


Fig. 2 (experiment 2).—Tracing showing the rise in ureteral tension on bursting of the bladder (photograph when camera is set for figure 1).

water) in experiment 3 and 22 mm. of mercury (29.9 cm. of water) in experiment 4. It returned when the bladder was emptied, always with a definite rise in tension and with increased frequency but diminished amplitude. The blue-stained distending fluid did not appear in the glass arm of the cannula or from the stump of the right ureter.

*Comment.*—Sudden distention of the bladder to a pressure in excess of 22 mm. of mercury (30 cm. of water) caused abrupt cessation of peristalsis in the ureter. Release of the intravesical tension caused a return of peristalsis, with a slight rise of tension. An inquiry into the mechanism which stopped peristalsis seemed in order.

EXPERIMENTS 5 and 6.—It was suspected that powerful contraction of the wall of the bladder as a result of the strong stimulation of rapid distention was involved. In these experiments the procedure was the same as in the preceding four, except that, following cannulation of the ureter, the lower end of the incision in the abdomen was left open and the bladder was allowed to protrude so that it could be observed.

When the bladder was distended, in neither case was there any significant change in the rate or the amplitude of the peristalsis (fig. 3). There was a slight fall in pressure, which returned to its previous level when the bladder was emptied.

It is to be noted that the curve of the pressure in the bladder was much different from that in the previous experiments, being much flatter; the maximum reading was lower, and respiratory variations were absent.

The wall of the bladder was stimulated electrically while the bladder was empty and again while it contained a small amount of fluid. Although the pressure rose to between 20 and 25 mm. of mercury (from 27 to 34 cm. of water), no cessation of peristalsis occurred. No blue fluid appeared in the arm of the cannula or in the abdomen.

Comment.—Apparently the cessation of peristalsis which accompanied vesical distention did not depend on contraction of the wall of the bladder.

In order to test whether this cessation of peristalsis was a reflex excited by stretching of the wall of the bladder, the last two animals were again used in experiments 6 and 7.

EXPERIMENTS 7 and 8.—A sterile, inelastic cloth bag having a capacity of 150 cc. was slipped over the bladder, which was allowed to protrude from the open incision. Distention of the bladder still failed to influence the ureteral peristalsis, although the pressure was raised to 200 mm. of mercury (272 cm. of

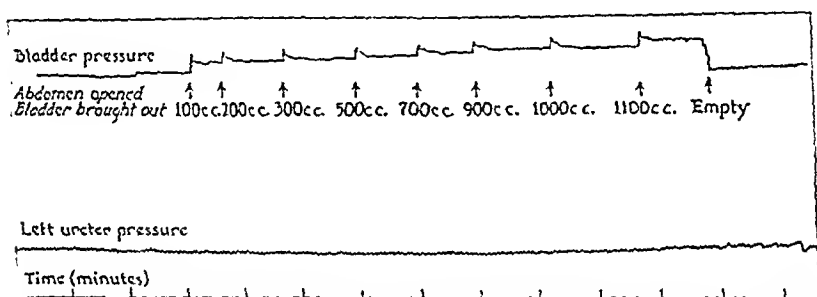


Fig. 3 (experiment 5).—Tracing showing that peristalsis was not influenced by distention of the bladder while it protruded from an abdominal incision.

water), a procedure which caused multiple hemorrhages in the wall of the bladder. No blue fluid appeared in the side arm of the ureteral cannula or from the right side.

*Comment.*—Apparently this phenomenon was independent of the absolute tension in the bladder, but depended on some other factor. Since it had been noted that the bladder of the dog, when rapidly distended, always produced bulging of the abdominal wall, even when the fluid content was small, it was suspected that the cessation of peristalsis might depend on a reflex excited when the full bladder impinged on the abdominal wall.

EXPERIMENTS 9 AND 10.—The animals used in these experiments were normal males weighing 9 and 11 Kg., respectively. Distention of the bladder caused disappearance of peristalsis when pressures of 22 and 24 mm. of mercury (30 and 32 cm. of water), respectively, were reached. The cloth bag already described was slipped onto the bladder, and the abdomen was closed. When the tension in the bladder reached the previous level, the lower part of the abdominal wall could be seen to bulge; peristalsis ceased. Emptying the bladder resulted in a return of peristalsis, accompanied by a rise of pressure in the ureter.

The abdomen was reopened. While the bladder was empty, traction was made with the finger on the peritoneum at the edge of the abdominal incision. Peri-



stalsis ceased, but returned when traction was abandoned. The usual slight rise of pressure accompanied the return of peristalsis. At no time did blue fluid appear in the arm of the ureteral cannula or in the abdomen.

*Comment.*—It seemed safe to conclude that the cessation of peristalsis which accompanied vesical distention was due to a reflex excited by compression or stretching of the portion of the abdominal wall which was compressed by the distended bladder.

It had been noted that, although urine appeared to flow from the ureter into the bladder in all experiments until the vesical distention stopped peristalsis of the ureter, the recorded pressure in the bladder always exceeded that in the ureter. In order to investigate this apparent paradox, experiments 11 and 12 were performed.

EXPERIMENT 11.—In a male dog weighing 13 Kg. the right ureter was cut, and the vesical end was tied. The left ureter was cannulated in the usual fashion,

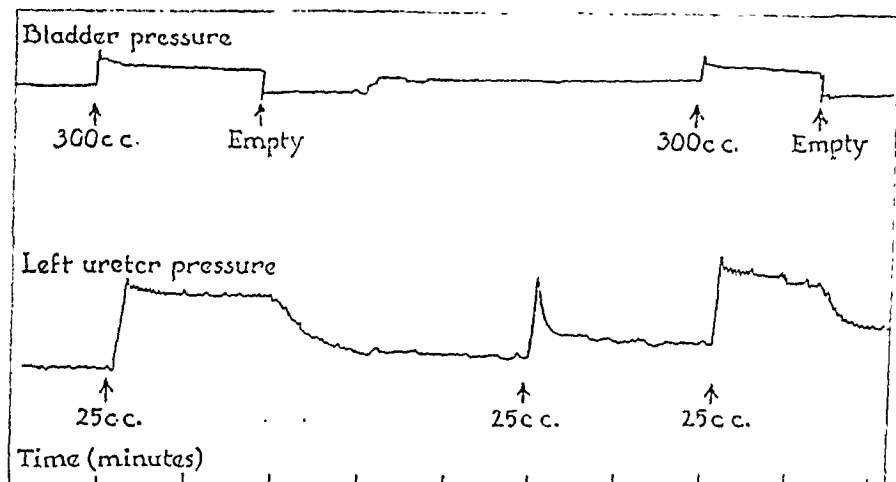


Fig. 4 (experiment 11).—Tracing showing how the pressure developed in the ureter by the injection of saline solution fell with the development of peristalsis (photograph when camera is set for figure 1).

but clear saline solution was used to fill the bladder and indigoindisulphonate was given intravenously to color the urine which came down the ureters.

When 200 cc. of fluid had been injected into the bladder, the tension was 23 mm. of mercury (31 cm. of water), while the ureteral pressure was only 4.7 mm. of mercury (6.4 cm. of water). Yet when the fluid from the bladder was withdrawn, it was blue from the first, indicating that urine had been passing into the bladder.

A small amount (25 cc.) of sterile saline solution was then injected slowly into the ureteral cannula. A prompt rise of pressure resulted (fig. 4). Peristalsis increased in amplitude, and a slight fall in the tension in the ureter occurred. When the bladder was emptied, the pressure fell rapidly, but not to the base line. A second injection into the ureter resulted in a sharp rise in pressure, which fell almost at once. Refilling of the bladder was followed by injection of the ureter. The ureteral pressure now fell very slowly until the bladder was emptied, when it dropped rapidly. At no time did the pressure in the ureter equal that in the bladder, even though urine could be shown to be passing into the bladder.

EXPERIMENT 12.—This was a repetition of the foregoing experiment, except that no indigotindisulphonate was given intravenously, but was injected into the ureter instead. It stained the fluid of the bladder while the tension in the ureter was below that in the bladder. Injection into the ureter was followed by a rapid fall of pressure in the ureter if the bladder was empty and by a slow decline if it was distended. Only when the bladder was empty did the pressure in the ureter exceed that in the bladder. Yet blue-stained irrigating fluid appeared in the bladder, even when it was distended.

*Comment.*—The apparent paradox of water passing from an area of low to one of higher pressure is explicable only on the basis of the functional ability of the ureter. As Lucas<sup>5</sup> demonstrated, the isolated ureter of the dog can sustain a pressure of 92 cm. of water. It is easy to see, therefore, how the segment of the ureter between the cannula and the bladder can generate sufficient pressure to force the urine into the bladder. The cannula was at the level of the iliac vessels so that an inch or more of ureter was available for creating the necessary force.

It is to be noted that thus far no reflux of the stained contents of the bladder had occurred, either into the glass arm of the cannula or into the vesical stump of the right ureter.

After the determination of what happens when the bladder is distended rapidly, a standard thereby having been set up, it seemed desirable to determine whether acute urinary retention altered the response of the bladder or ureter to distention of the former.

*Method.*—Normal male dogs excreting normal, sterile urine were used. The urethra was ligated in the perineum with linen tape under local anesthesia, and with sterile precautions. The animals were placed in cages designed for measuring the metabolism to permit one to be certain that no urine escaped. After retention had been established, the investigations already described were repeated.

EXPERIMENT 13.—A male dog weighing 12 Kg. was used. After twenty-four hour retention, the abdomen was opened under morphine and procaine hydrochloride anesthesia. The bladder was greatly distended and cyanotic. There were no visible hemorrhages in its wall. It was surrounded by warm, moist bowel, and was dislocated through the incision. A rubber-shod clamp was placed upon the left ureter just above the iliac vessels; the ureter was cannulated and connected to the water manometer. The vesical end of the right ureter was cannulated. The abdomen was closed, with the handles of the rubber-clad clamp protruding. The urethral ligature was removed, and a rubber catheter was passed into the bladder and tied. It was at once connected to the mercury manometer, without the loss of urine. The clamp was then removed from the ureter.

The pressure in the bladder was 8 mm. of mercury (10.9 cm. of water); distention of the bladder produced, at a tension of 21 mm. of mercury (28.0 cm. of water), abrupt cessation of peristalsis; on emptying the bladder peristalsis returned, with a definite rise of pressure. These changes could be reproduced at will.

At no time did the irrigating fluid appear in the side arm of the T-cannula or from the vesical stump of the right ureter.

EXPERIMENT 14.—A dog weighing 20 Kg. was used. After urinary retention of forty-eight hours' duration the bladder was hugely distended and was cyanotic, with hemorrhages in the posterior wall. Connection of the left ureter and the bladder to manometers was accomplished without loss of fluid. Tracing of peristalsis began at once. The pressure was 12 cm. of water (fig. 5). The bladder was flaccid. One hundred cubic centimeters of blue irrigating fluid was injected. The pressure in the ureter had been rising gradually before the injection and

continued to do so. Some diminution in the peristaltic rate was noted. The withdrawal of 70, then 50, cc. of urine caused a slight fall in ureteral tension. The bladder was emptied suddenly. The pressure in the ureter fell to zero; the peristalsis increased in rate, but its amplitude diminished. No reflux was observed. The animal was killed for anatomic studies.

**EXPERIMENT 15.**—This experiment was a duplicate of the preceding one. The bladder was distended and cyanotic and showed hemorrhages in the posterior wall. When manometers were connected, the pressure in the bladder and that in the ureter were 20 and 17.4 cm. of water, respectively. On the addition of 200 cc.

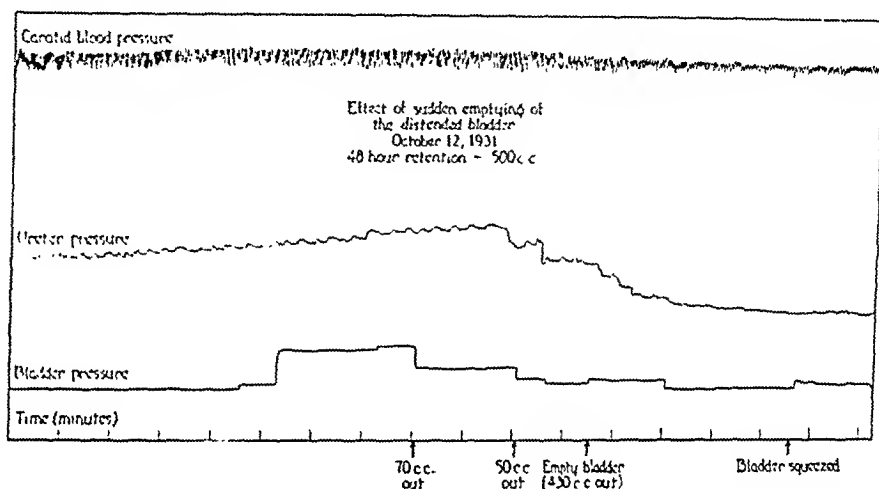


Fig. 5 (experiment 14).—Effect of sudden emptying of the distended bladder (500 cc.) after forty-eight hour retention on ureteral peristalsis.

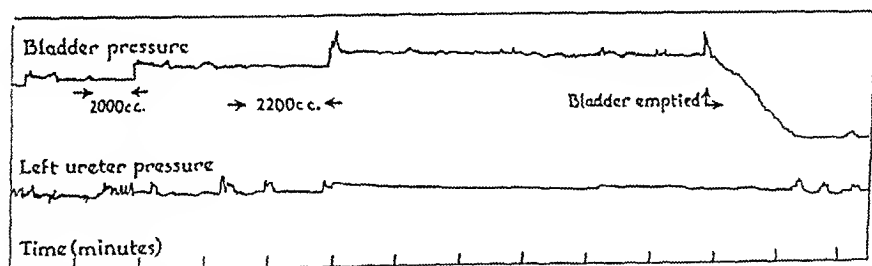


Fig. 6 (experiment 15).—Tracing showing cessation of ureteral peristalsis on further filling of a bladder already obstructed for forty-eight hours; peristalsis returned on emptying the bladder.

of blue irrigating fluid to the contents of the bladder, the peristalsis of the ureter diminished in frequency. On the injection of another 200 cc. it ceased. Withdrawal of the contents of the bladder (2,200 cc.) was followed by a return of peristalsis of a very low frequency (fig. 6). There was no rise in pressure.

No regurgitation up either ureter could be detected.

**EXPERIMENT 16.**—A male dog weighing 18 Kg. was used. The experiment was a duplicate of experiment 14, except that the retention was maintained for seventy hours. The bladder was enormously distended and was hemorrhagic and gangrenous. The tension in the bladder was 8 cm. of water, and in the ureter

4 cm. Peristalsis was active. It was inhibited by the injection of fluid into the bladder and reappeared, without a rise of pressure, on emptying the bladder. No regurgitation of fluid up either ureter could be seen.

*Comment.*—The mechanism causing inhibition of ureteral peristalsis during sudden rises of the intravesical tension persists for as long as seventy hours after the development of urinary retention. Experiments were discontinued at that time because previous work had shown that the bladder invariably ruptures at about seventy hours. The persistence of this mechanism after the extreme disorganization of the wall of the bladder in seventy hour retention fortifies the initial view that the reflex depends on some extravescical mechanism.

#### GENERAL COMMENT

If the statements in the literature are true, water can run uphill, in so far as it appears to pass from an area of negative pressure (the renal pelvis) to an area of positive pressure (the urinary bladder). To accomplish this feat, nature has evolved an ingenious mechanism and has taken many precautions to protect the kidney against regurgitation of urine from the bladder.

As has been pointed out, the pressure in the pelvis is usually negative. As peristalsis drives the urine down the ureter, its pressure rises until it is positive by a few centimeters of water in the vesical end of the ureter. From here the urine passes into an active muscular reservoir, where the average tension is about from 6 to 10 cm. of water. The activity of this reservoir has been admirably gaged to prevent the too frequent development of high pressures and consequent damage, by permitting it to maintain a constant degree of pressure within wide limits of filling—the postural tone of Sherrington.<sup>28</sup>

To prevent the retrograde propagation of the pressure of the bladder a fourfold mechanism exists. The first factor, the ureterovesical valve of Sampson,<sup>21</sup> closes off the ureteral meatus mechanically when the vesical tension rises. This is supplemented by a second mechanism, the oblique course of the ureter in the wall of the bladder (Israel<sup>32</sup>). This arrangement is such that contraction of the detrusor urinae constricts the ureter, an effect which is augmented by the anteroposterior compression resulting from the intravesical tension. A third factor has received little emphasis but is probably equal in importance to the first two, namely, ureteral peristalsis. Pflaumer<sup>37</sup> and others have shown by means of intravenous urography that the normal ureter is probably never entirely filled throughout its length, but is divided into segments by peristaltic contractions. As has been already pointed out, the individual peristaltic wave may, on occasion, generate a very high pressure (71 mm. of mercury, or 96.5 cm. of water) and may resist a distending pressure of 92 cm. of water. Thus, it would appear that this mechanism alone would suffice to prevent the regurgitation of urine from the bladder to the kidney, except during prolonged and powerful straining.

This ability of the ureter to produce high pressures explains the apparent discrepancy between the tension in the pelvis and ureter and that in the bladder. It is apparent that a short segment of the ureter can generate a high tension without causing any rise a short distance above it. This is the only basis on which one can account for the observations in experiments 11 and 12, in which, in spite of the fact that the intravesical tension exceeded that in the ureter during the whole period of observation, urine flowed into the bladder. It is undoubtedly this mechanism which prevents dilatation of the ureter and renal pelvis during the early stages of chronic urinary retention.

The efficiency of these mechanisms is great, if one may judge from the literature. The fact that urinary reflux is almost never observed in the normal dog or human being, while occurring with great regularity in the rabbit, emphasizes, as Gruber<sup>52</sup> has shown, the importance of the oblique course of the intramural ureter.

The results of this series of experiments corroborate the view that reflux is rare in the dog, since it was never observed either during rapid distention or stimulation of the normal bladder (experiments 1 to 10) or during rapid distention or stimulation of the bladder after complete retention lasting as long as seventy-two hours.

A fourth protective mechanism, which has apparently not been described previously, was demonstrated by the foregoing series of experiments, namely, a reflex which stops ureteral peristalsis when the intravesical tension rises suddenly (experiments 1 to 4, 7 to 10 and 13 to 16). A need for this reflex exists. While the backward transmission of pressure in the normal urinary tract is effectively prevented, a dangerous situation might nevertheless develop if a high vesical tension were present for any length of time, owing to the ability of the kidney and ureters to produce pressures as high as 70 mm. of mercury (95 cm. of water). It is clear that if a high vesical tension persisted the upper urinary tract would build up a tension sufficient to interfere with its own venous return and thus to cause serious lesions. It is undoubtedly this mechanism which produces the renal and ureteral hemorrhages in experimental acute retention as well as those occurring after ligation of the ureter.

That it is a reflex which arises outside the wall of the bladder is shown clearly by experiments 5 and 6, in which ureteral peristalsis persisted in spite of electrical stimulation of the wall of the bladder, and by experiments 14 to 16, in which peristalsis stopped on distention when the bladder was so badly damaged by retention that it could not contract spontaneously. Experiments 7 to 10 prove that stretching of the wall of the bladder, with the resultant stimulation of the vesical nerves, plays no part in its production.

Its dependence on the nerves of the abdominal wall was first suggested by the visible forward bulging of the bladder during distention of sufficient degree to arrest ureteral activity. This view is verified by experiments 5 to 8, in which bringing the bladder out of the abdomen, while it failed to alter ureteral peristalsis, did prevent its arrest by vesical distention, and by experiments 9 and 10, in which the reflex was excited by traction on the parietal peritoneum.

The period during which this reflex protects the upper portion of the urinary tract has not been determined accurately, but in experiments 13 to 16 and during a long series of experimental acute retentions previously reported<sup>58</sup> it was found that the kidneys and ureters remained normal for twenty-four hours invariably, and for forty-eight hours in some instances, after urethral ligation. From this it may be inferred that the mechanism fails at some time between twenty-four and forty-eight hours after the onset of retention. Further evidence of its efficiency is obtained from the rapidity with which renal lesions develop after ligation of the ureter. Fabian<sup>8</sup> found edema of the peripelvic fat fifteen minutes after ligation of the upper ureter and hemorrhage within three hours. Helmholtz and Field<sup>10</sup> ligated the ureter lower in the rabbit and observed edema within four, and hemorrhages within eighteen, hours.

It is my belief, as yet not proved, that the damage in acute retention is due not to sustained high pressure but to the intermittent attempts to void, which may produce remarkable rises in intravesical tension, a supposition which would explain why this reflex may persist so long and prove to be so effective.

#### SUMMARY AND CONCLUSIONS

1. The literature on pressure relations in the urinary tract has been reviewed. The fact that intravesical tension is usually higher than the pressure in the renal pelvis and that the maximum pressure attainable by the bladder exceeds that attainable by the renal pelvis and ureter combined necessitates some mechanism to protect the kidney against the bladder.

2. The literature describes a threefold mechanism for this purpose, consisting of the ureterovesical valve of Sampson, the oblique course of the ureter through the wall of the bladder and the peristaltic contractions of the ureter. The last-mentioned factor is probably more important than one would suspect from the literature, since a short segment of the ureter can develop a pressure of 90 cm. of water and can resist a similar distending pressure.

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58. Creevy, C. D.: Distention of the Urinary Bladder: I. Hematuria and Sudden Emptying; Experimental and Clinical Study, Arch. Surg. 28:948 (May) 1934.

3. A series of 16 experiments on the dog has revealed the existence of a fourth protective mechanism, a reflex which stops ureteral peristalsis during periods of sudden increase in the intravesical tension.

4. This reflex is excited not through the nerves of the bladder but through stimulation of the anterior abdominal wall by the bulging forward of the distended bladder. It persists even when the bladder is badly damaged by intramural hemorrhage.

5. Back pressure probably does not exist in the normal urinary tract of the dog, since the reflux of urine does not occur during sudden distention of the bladder, even after long-standing acute retention. Instead, the injurious pressure is generated by the kidneys and ureters in an attempt to force urine into a distended bladder.

6. The purpose of the reflex seems to be to protect the upper portion of the urinary tract against its own rise in tension during sudden sharp rises in intravesical pressure.

7. The reflex is evidently successful for periods of from twenty-four to forty-eight hours, since the kidneys and ureters remain normal up to that time during acute retention of the urine.

### III. BACTERIOPHAGES IN TREATMENT OF COLON BACILLUS SEPTICEMIA

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Septicemia due to the colon bacillus, though less common than septicemia due to the cocci, is ordinarily a disease of high mortality. It arises as a terminal phase of an ascending urinary infection and less frequently by extension of septic infection from other regions of the body. During the past three years we have seen and treated three patients with this condition and have had the opportunity to furnish bacteriophage preparations and advice as to their application for two other patients.

The cooperation of the patient, the clinician and the bacteriologist in this small group has presented a sharp contrast when compared with that experienced with the larger group of patients with urologic diseases. The patient with septicemia is usually in sufficient distress that he and his family are willing to follow the advice of the physician; and after a succession of positive blood cultures coupled with severe chills, sharp spikes of temperature, toxic psychic manifestations and other alarming signs and symptoms have been observed, the clinician is more inclined to welcome any possible aid which may be offered by modern laboratory service. The serious nature of the disorder also challenges the best efforts of the laboratory worker, who senses the enhanced valuation of his own work in relation to these more desperate clinical problems and is thus stimulated to superlative effort.

The records for four of these patients are quite complete, and they will be presented here in summarized form. The fifth patient came under observation during the preparation of this paper, and the record is not yet available for presentation.

#### REPORT OF CASES

CASE 1.—M. L., a white woman, aged 21, admitted to the hospital on March 16, 1931, has been mentioned in earlier publications from this department, and her case was selected as the example of this group to be used in the more general discussion<sup>1</sup>

These studies have been aided by a grant from the Josiah Macy Jr. Foundation. From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

1. MacNeal, Ward J.: Specific Treatment of Septic Infections, Particularly with Aid of Bacteriophages, *Am. J. M. Sc.* 189:623, 1934.



of septic infections presented before the Section on Pharmacology and Therapeutics at the meeting of the American Medical Association at Milwaukee, June 16, 1933. It will suffice here to state that she suffered from pelvic thrombophlebitis, following an abortion, with repeated blood cultures positive for the colon bacillus. Following intravenous bacteriophage therapy she made a complete recovery and was discharged in excellent condition on April 28, 1931. This is probably our most striking example of apparent success in the treatment of colon bacillus septicemia with bacteriophage.

CASE 2.—G. J., a white woman, aged 43, suffered from an infection in her right foot from June 15 to June 25, 1932. As this was healing she began to have chills and fever, with a rise of temperature to 105 F. A blood culture taken on June 25 and brought to our laboratory gave abundant growth of colon bacilli, variety communis, in two flasks of broth and in three agar plates. A diagnosis of pyelitis was made, and after treatment with methenamine for ten days she was much improved. However, on July 21 she fell in a faint while walking toward the door of her room, and from that time she was weak and dizzy. On July 26 and 27 she had auditory and visual hallucinations, and on July 28 there was increasing drowsiness until she was admitted to the hospital in a comatose condition at 9:15 p. m., July 28.

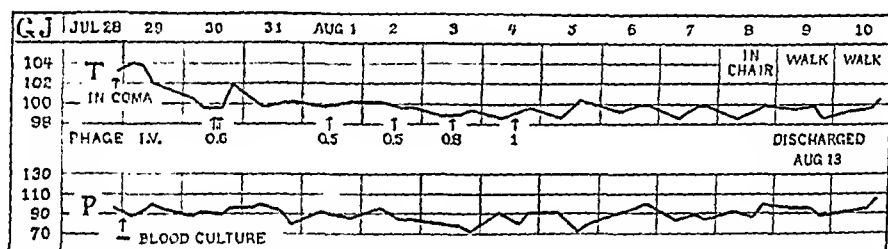


Chart 1 (case 2).—Abridged clinical chart for G. J., showing the course of the temperature (T) and pulse rate (P), together with outstanding features of the clinical record.

At this time the clinical diagnosis was bacteremia and probable septic thrombosis of the brain.

The clinical course in the hospital is indicated in chart 1. A blood culture taken at midnight on the day of admission remained sterile; a catheterized specimen of urine revealed red blood cells and pus; the blood chemistry and the spinal fluid were normal. Gastric lavage was done, and an infusion of 1,850 cc. of 5 per cent dextrose was given intravenously before 2 a. m. The patient remained unconscious and incontinent throughout the night. During the next day, July 29, she received 1,450 cc. of saline solution subcutaneously. She remained incontinent and unresponsive. On July 30 she became more alert and occasionally conversed in a rational manner. Most of the time, however, she was disoriented, sometimes being very noisy, and she required constant physical restraint in bed. A clysis of 1,000 cc. was given just before noon.

On this day bacteriophage treatment was urgently requested by the patient's physician, who regarded the prognosis as grave. In regard to bacteriology, we had only the evidence seen in a fresh specimen of urine in addition to the positive blood culture obtained on June 25, before the patient's admission to the hospital. However, the chemical analysis of the blood, which had been repeated, disclosed nothing to explain the mental derangement, and it was decided that the possibility of benefit overbalanced the dangers. Therefore, to obtain prompt effect,

the stock asparagine preparation of colon bacteriophage was given intravenously. 1 cc. of a 1:10 dilution at 1:45 p. m.; a second dose of 2 cc. at 2:37 p. m. and a third dose of 3 cc. at 3:18 p. m., on July 30. There was no chill following these injections, and only a moderate rise in temperature to 102 F. at 8 p. m. The next day she was rational but not cooperative. The day being Sunday, one of the physicians had told her that she would not receive any intravenous injections, and when we arrived at the hospital to give her a treatment she emphatically refused to permit it. However, on Monday and the following days she readily submitted to the intravenous therapy, which was discontinued as no longer required after August 4. Intravesical bacteriophage treatment was advised but was refused by the patient, who insisted that she was well enough to go home. A culture of the urine on August 2 yielded 23,000,000 colonies of colon bacilli per cubic centimeter. The organism was a colon bacillus of the communis variety and only partially susceptible to the stock bacteriophage. Without further bacteriophage treatment the patient left the hospital on August 13 and was advised to continue taking methenamine. She came to the laboratory after about a month to inquire about obtaining bacteriophage for further treatment at home and was advised to be admitted again to the hospital for a thorough course of treatment of the

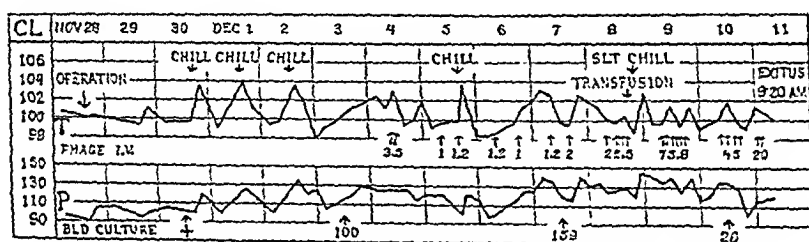


Chart 2 (case 3).—Abridged clinical chart for C. L.

persisting urinary infection. This she declined to do because she did not feel ill enough to make such a sacrifice.

As an example of successful bacteriophage therapy this case is not very satisfactory. The positive blood culture of June 25 contained the same type of colon bacillus found in the urine after the patient's admission to the hospital more than a month later. During the interval the patient had been up and about for part of the time. When admitted to the hospital on July 28 she seemed to be in a dying condition, but the blood culture taken at this time remained negative. Her clinical condition progressively improved, and during part of this period of improvement the colon bacteriophage was injected intravenously. She as well as her physicians ascribed the improvement in large measure to the use of the bacteriophage. One may justly be skeptical about the relationship. Because of lack of cooperation by the patient it was impossible to carry out thorough treatment of the infection of the urinary tract.

CASE 3.—C. L., a man, aged 66, had been under treatment for long-standing osteomyelitis of the legs and chronic septic inflammation of the knee joint which had been incised in 1917. On Nov. 28, 1932, a suprapubic prostatectomy was performed. His subsequent clinical record is summarized in chart 2. Following this operation septic fever developed, and the blood culture taken on November 30 yielded colon bacilli. On December 2 the patient was dyspneic. The area of cardiac dulness was enlarged, and there were occasional premature beats. The

blood pressure was 120 systolic and 57 diastolic, and the pulse rate varied from 100 to 135. Coarse râles, squeaks and rhonchi were heard over both lungs, and the squeaks were much diminished after injection of epinephrine. There was evidence of marked arteriosclerosis. A second blood culture taken on December 3 yielded about 100 colonies per cubic centimeter. Bacteriophage therapy was requested on December 4 and promptly initiated by an intravenous injection of 4.3 cc. of a 1:10 dilution of the stock asparagine preparation of colon bacteriophage at 10:04 a. m. This was followed by the administration at 11:12 a. m. of 1 cc. of the undiluted phage intravenously and at 12:13 p. m. of 2.1 cc. of the undiluted phage intravenously. On December 5 he was given an intravenous injection of 1 cc. at 8:15 a. m. and another of 1.2 cc. at 4:05 p. m., which was followed twenty-five minutes later by a chill and a rise of temperature to 103.8 F. at 5 p. m., profuse diaphoresis at 9 p. m. and a drop of temperature to 98.4 F. at midnight. On December 6 he received an intravenous injection of 1.2 cc. of the stock asparagine preparation of bacteriophage at 8:35 a. m. and at 5:10 p. m. 1 cc. of a newly prepared specific bacteriophage in asparagine, representing the filtrate of the lysed bacterial culture isolated from his own blood stream. On December 7 he received 1.2 cc. of the specific phage intravenously at 7:45 a. m. A blood culture was taken at noon, and at 3:55 p. m. another intravenous injection of 2 cc. of the specific bacteriophage was given. On December 8 the many colonies already appearing in the blood culture of the preceding day indicated the futility of the bacteriophage treatment up to that time. Five intravenous injections of the specific bacteriophage were given on this day: 2.5 cc. at 8:05 a. m., 3 cc. at 12:35 p. m., 4 cc. at 1:42 p. m., 5 cc. at 3:06 p. m. and 8 cc. at 4:45 p. m., making 22.5 cc. for the day. He was also given a transfusion of 400 cc. of blood at 5:24 p. m. A slight chill at 8:15 p. m., with a rise of temperature to 102.8 F. at midnight, may have been related to the transfusion or to the bacteriophage or to both. On December 9 the condition was clinically so critical that the dosage of bacteriophage was further increased: 9.7 cc. at 8:15 a. m., 9.1 cc. at 9:35 a. m., 10 cc. at 10:45 a. m., 10 cc. at 12:30 p. m., 15 cc. at 2:58 p. m., 10 cc. at 4:13 p. m. and 12 cc. at 5:34 p. m., making a total of 75.8 cc. for the day. There was no evident chill or significant rise in temperature which could be ascribed to these intravenous injections, and the general condition remained unsatisfactory. There were labored respiration, an irregular pulse and increasing edema of the extremities and trunk. On December 10 he received four intravenous injections of specific bacteriophage: 11 cc. at 9:20 a. m., 12 cc. at 11:55 a. m., 12 cc. at 3:20 p. m. and 10 cc. at 5:20 p. m., making a total of 45 cc. for the day. Through some misunderstanding the subsequent prescribed doses were omitted until after midnight. Two doses of 10 cc. each were then given, one at 1 a. m. and the next at 3 a. m. Respiration ceased at 9:14 a. m. The blood culture taken at 11:45 a. m. on December 10 yielded 26 colonies per cubic centimeter of blood, and the bacteriophage was recovered from the broth of this blood culture.

CASE 4.—A. C. T., a white woman, aged 25, was admitted to the service of Dr. Eugene Dalton at the Methodist Episcopal Hospital in Brooklyn on Dec. 31, 1932. We are indebted to the house physician, Dr. Hugh K. Miller, for the records. The patient, married in July 1932, was at the end of the fourth month of her first pregnancy, which had been free from disturbances except for morning sickness on one day in October, incontinence of urine since July and frequency of micturition since August, with nocturia, the patient urinating three or four times each night, up to December 26. On this day she began to have headache and severe vomiting, which became continuous. On December 29 she began to cough. Examination of the urine before admission revealed pus cells. On admis-

sion (December 31) the temperature was 104 F., the pulse rate 120 and the respiratory rate 36; the abdomen was enlarged, and the uterine fundus extended 130 mm. above the symphysis; there were marked tenderness in the left flank and slight pharyngitis. The urine on Jan. 1, 1933, revealed leukocytes and erythrocytes. The blood count showed 15,500 white cells with 91 per cent polymorphonuclears. Vomiting, which had persisted up to this time, ceased on January 2. A blood culture taken on January 3 revealed colon bacilli, and another blood culture taken on January 5 showed abundant colon bacilli the next day. A transfusion

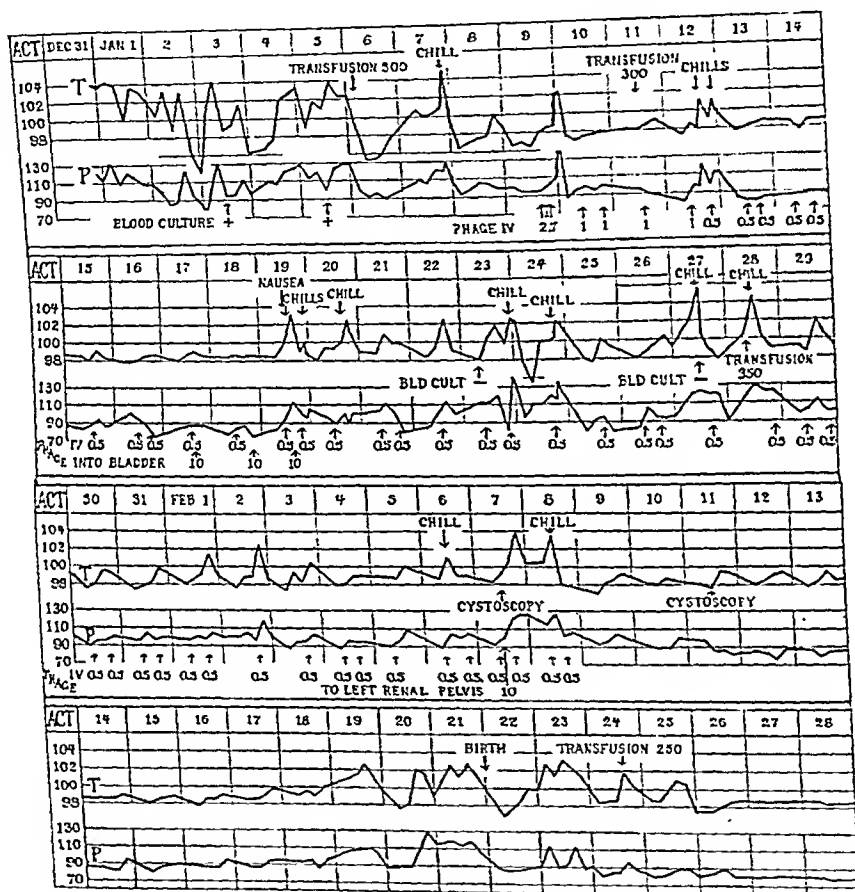


Chart 3 (case 4).—Abridged clinical chart for A. C. T.

of 300 cc. of blood was given on January 6; one of 300 cc. on January 11; one of 350 cc. on January 28, and one of 250 cc. on February 24. Bacteriophage treatment was begun on January 9, on which day four intravenous injections of the asparagine preparation were given, the total amount being 2.7 cc. The intravenous administration of bacteriophage was continued in smaller doses every day until February 8. The reaction of the urine was adjusted, beginning on January 16, by oral administration of potassium citrate, controlled by daily determination of the  $p_n$  of the urine, which remained between 6.6 and 7.2 after January 19. Ten cubic centimeters of the broth preparation of bacteriophage diluted with saline solution was introduced into the bladder on January 17, 18 and 19, and bacterio-

phage was introduced into the left renal pelvis on February 7. The clinical chart suggests that these local applications were not particularly beneficial to the patient. The blood chemistry revealed no abnormalities at any time. The most extreme leukocytosis was observed on January 28, when there were 30,700 white cells and 80 per cent polymorphonuclears together with 12 per cent metamyelocytes. A blood culture taken on January 23 and another taken on January 27 remained negative. The urine cultures, however, remained persistently positive for colon bacilli on January 10, 13, 16 and 26 and February 1. A roentgenogram on January 24 revealed slight enlargement of the left kidney.

Because of the persistent urinary infection and absence of other serious disease, the patient was transferred to the urologic service in the same hospital on February 7, in good general condition. A pyelogram made on February 7 revealed dilatation and kinking of the left ureter, dilatation of the left renal pelvis and questionable evidence of a calculus in the left kidney; on the right side there was slight dilatation of the ureter and the renal pelvis. Urine from the left ureteral catheter gave a growth of colon bacilli, as did that from the bladder. Urine from the right ureteral catheter was negative on culture. Bacteriophage was introduced into the left renal pelvis on February 7 after the specimens had been taken. Ureteral catheterization on February 11 showed sterile urine coming from both renal pelves, but the bladder urine still contained colon bacilli and an excessive number of leukocytes.

On February 21 the patient went into labor. A boy was delivered at 12:10 a. m. on February 22 and died at 1:22 a. m. After an uneventful puerperium, the patient was discharged from the hospital free from symptoms on March 5.

The patient came to the laboratory at the New York Post-Graduate Medical School and Hospital on March 30, and we obtained a satisfactory uncontaminated specimen of urine from the bladder. This contained moderately numerous pus cells and rod-shaped bacteria, and cultures of it revealed 15,000,000 colonies per cubic centimeter. The organism proved to be a colon bacillus of the communis variety, similar to that obtained in the earlier blood cultures. It was recommended to her physician that an attempt to eradicate the infection from the urinary tract be undertaken. The patient was free from distressing symptoms but appeared rather thin and weak at the time of her visit. Apparently she, as well as her relatives, wished to postpone further treatment for a time.

CASE 5.—This patient was in the Morrisania Hospital, service of Dr. Clarence H. Smith. Repeated positive blood cultures were obtained. A radical operation on the mastoid with removal of a septic thrombus from the lateral sinus and from the jugular vein revealed in these situations the same colon bacillus as was found in the blood stream. The colon bacteriophage was given by intramuscular and intravenous injection and by local application to the wound. The patient died about June 14. The autopsy revealed extensive pneumonia and purulent pyelitis. Further details in regard to this case are not yet available.

#### COMMENT

From this rather limited experience we feel justified in urging the intravenous use of an asparagine preparation of colon bacteriophage in colon bacillus septicemia. In four of these cases the microbe present in the blood stream was found to be susceptible to lysis by our stock colon bacteriophage. In the fifth case (Dr. Smith's) the bacteriologic studies were carried out elsewhere, and we did not have opportunity for ade-

quate study of the infecting microbe. These findings suggest that organisms of this group virulent enough to produce septicemia are in general more likely to prove susceptible to bacteriophage than those found in the intestine or in the urinary tract. Whether there is an actual correlation between the virulence of the microbe and its susceptibility to bacteriophage cannot be decided from this evidence alone, but the suggestion appears to be of some interest.

It seems wise to begin treatment with a stock bacteriophage as soon as the specific nature of the organism in the blood culture has been recognized. At the same time, the testing of this culture against the bacteriophage and the preparation of a specific bacteriophage by filtration of lysed cultures of the specific microbic strain should be pushed as rapidly as possible in the laboratory, and as soon as such a specific preparation is ready it should be used in place of the stock bacteriophage.

#### SUMMARY

Septicemia due to the colon bacillus is a disorder of sufficient gravity to invite effective cooperation in its treatment.

The control of the bacteremia appears somewhat easier in the case of the colon bacillus than in the case of the staphylococcus.

Of the five patients observed, one made a complete recovery; two recovered from the bacteremia and left the hospital with persistent bacilluria, and two died.

Bacteriophages potent against colon bacilli may, according to our limited experience, be of some assistance in the treatment of colon bacillus septicemia.

# IV. BACTERIOPHAGES IN CHRONIC COLITIS OF UNDETERMINED CAUSATION AND IN INTESTINAL FISTULAS

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In an earlier paper we emphasized the need of specific etiologic diagnosis as a prerequisite for the intelligent use of bacteriophages in the treatment of infections. This point of view requires no defense. It is well, however, to recognize that human disease may not infrequently present a problem which defies satisfactory scientific elucidation and that the physician may be required to assume the responsibility for the treatment of a patient whose disorder is only imperfectly understood.

We feel that some apology is required as an introduction to the discussion of the application of bacteriophages in the treatment of the often obscure, nonspecific types of chronic inflammation of the large intestine and of fistulous tracts through which are passing the multitudes of intermingled micro-organisms and heterogeneous remnants of food in the human feces. In some instances it may be possible to recognize among the microbes an individual species of outstanding importance in the causation of the active infectious process, as for example *Shigella dysenteriae*, the endameba of dysentery or the tubercle bacillus. Certainly the search for these specific causative agents should not be neglected, and when one or the other is detected this knowledge becomes paramount as a guide in combating the disease. Unfortunately, particularly in the bacillary dysenteries, the original specific microbic agent is detected with difficulty after the first few weeks or even after the first week of the disease. Apparently its numbers are greatly reduced, and it appears reasonable to assume that the continuing inflammatory process is caused in part by secondary invaders, intestinal bacteria ordinarily harmless to the intact intestinal wall, but injurious to the deeper structures after the integrity of the protective epithelial covering has been disturbed. The varieties of colon bacillus and staphylococcus appear

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These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

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readily to take up the rôle of secondary invaders. The human intestinal flora is a mixture of various microbes from the early days of extra-uterine life. One may therefore find some justification for the idea that by overcoming a few of these microbic species or even only one of them it may be possible to change conditions at the site of the lesions so that the balance may be tipped in the direction of healing. On ideas such as this one attempts to base an excuse for the empirical use of bacteriophages in nonspecific intestinal inflammations and fecal fistulas and in such argument to find a reason for the occasional success which follows the treatment. But even in the absence of a logical explanation or excuse a favorable factor in the treatment of an afflicted human being makes an emotional appeal which may defy intellectual opposition, a situation which gives long life to quackery and charlatanism. We are conscious that the case records to be presented may expose us to some unfavorable criticism on this score, which does not, however, give us great concern.

#### CHRONIC COLITIS

We have records of fourteen patients who suffered from stubborn disease of the alimentary system, diagnosed as chronic colitis and treated with preparations of bacteriophage. In seven there was definite clinical improvement. In six the result of treatment has not been reported to us. One patient who is under observation was treated with bacteriophage for several months with little or no evidence of relief. Few of these patients have been under observation in the hospital, and on that account the records lack detail and precision. The available records of four of the more fortunate patients will be briefly presented in order to illustrate the methods of application of the bacteriophages and the course of the disorder.

#### REPORTS OF CASES

CASE 1.—E. S., a boy, aged 9½ years, a patient of Dr. Saul J. Selkin, was suffering from persistent diarrhea. The hemolytic colon bacillus of the variety communis was found predominant in the stool on Feb. 25, 1932, and after three serial filtrations a bacteriophage became fairly potent against this bacillus. The bacteriophage filtrate was mixed with other bacteriophages active against dysentery, proteus and pyocyaneus bacilli. The mixture was given by mouth three times a day in doses of 2 cc., and as retention colonic irrigation in doses of 10 cc. every forty-eight hours for a period of approximately two weeks. The patient was then much improved and returned to school. Subsequently he became entirely well. Further information in regard to this patient is not available.

CASE 2.—E. H., a white girl, aged 13 years, the daughter of a physician and a patient of Dr. E. F. Henderson of New Castle, Pa., had suffered from intractable ulcerative colitis for eight years. She had been under the care of various specialists. On March 24, 1932, we supplied a mixed bacteriophage to be taken by mouth in doses of 2 cc. On March 30 we received a specimen of the stool, the cultures of which yielded predominant colon bacilli of the lactic acid variety, streptococci



producing a narrow zone of hemolysis on blood agar and enterococci. The physician reported clinical improvement on April 4 and again on April 13. By April 25 the girl had gained 5 pounds (2.3 Kg.), and the number of stools was now two or three a day instead of from ten to fourteen a day. The bacteriophage was discontinued for one week, and the frequency of defecation again increased, the number of stools reaching ten a day. With resumption of the bacteriophage therapy a decrease occurred to two stools a day. The bacteriophage treatment was continued until the last of August, when it was stopped. During this time the girl was in better general health than at any time in eight years. In March, 1933, the physician reported that for the first time in her life the girl had attended school regularly since the previous fall and had gained 17 pounds (7.7 Kg.). She continued to take bismuth daily and was also taking cod liver oil. Dr. Henderson ascribes the improvement chiefly to the use of the bacteriophage. His judgment commands respect because of his intimate knowledge of the case over a period of many years.

CASE 3.—S. K., a white boy, aged 2 years and 5 months, was admitted on Aug. 4, 1931, to the service of Dr. R. H. Dennett. The child was born March 20, 1929, was breast fed for ten months, and developed in a normal manner until July 31, 1931, when he suddenly became ill with vomiting, diarrhea, restlessness and fever between 102 and 105 F. On the day preceding the onset of illness, the child ate six tomatoes, some corn and other foods. Bacteriologic examination of a stool passed on August 6 failed to disclose any dysentery organisms. The most abundant bacteria in the cultures were staphylococci, diphtheroids and colon bacilli of the *lactis-aerogenes* variety. On August 20 and 24 an examination for amebas, intestinal worms and eggs of worms yielded negative results. Many pus cells were present in the stools. A specimen obtained from the rectum by proctoscopy on August 31 yielded, on culture, predominating streptococci producing green colonies on blood agar. There were also abundant colon bacilli of the *lactis acid* and *lactis-aerogenes* varieties. The specific microbic factors in the illness were not disclosed by these laboratory studies.

The course of the temperature and pulse rate and number of stools each day are shown in chart 1. The child did not progress for the first five days. On August 8 a transfusion of 200 cc. of blood was given at 10:25 a. m.; at 3 p. m. on the same day broth of a bacteriophage mixture, 10 cc., mixed with milk, was given by mouth and a small retention enema containing 10 cc. of the bacteriophage mixture was introduced into the colon. The mixture was of the shotgun variety, composed of antidysentery bacteriophage, 2 parts, anticoli bacteriophage, 6 parts, and antiproteus, antistaphylococcus, antistreptococcus and antipyocyaneus bacteriophage, each 1 part. The material given by mouth was retained, but the enema was almost immediately expelled although the patient was in a bed set in the position for shock. In fact, the enema evidently irritated the sensitive mucous membrane of the rectum, which was already slightly prolapsed, so that the number of stools on this day rose to sixteen. However, improvement in the clinical condition of the patient and in the temperature and pulse rate seemed to begin immediately. On August 9 the bacteriophage mixture was again given by mouth in the milk: 10 cc. at 10 a. m. and again at 3 p. m. A retention enema containing 10 cc. of the bacteriophage mixture was again quickly expelled. Subsequently the bacteriophage was given only by mouth. The stools, previously watery and green or brown, showed some improvement, being at times yellow and occasionally semiformed, with visible mucus. However, the diarrhea continued, although the general condition of the child improved. Bacteriophage therapy was discontinued on August 26, and on August 27 the feeding formula was limited to evaporated

milk exclusively, which was supplemented with zwieback on September 5 and farina on September 7. After September 1 the diarrhea disappeared, and the patient was discharged in good condition on September 22. He returned to the outpatient department once a month until May, 1933, and during this interval had remained in good condition, with only occasional colds in the head.

CASE 4.—H. G., a white woman, aged 47, unmarried, was admitted to the Long Island College Hospital on Dec. 19, 1930, to the service of Dr. L. F. Warren.<sup>1</sup> Diarrhea and weakness had become progressively worse during the preceding three weeks. The weight on admission was 113 pounds (51.3 Kg.), which had been the normal weight. Examination of the stools for *Endamoeba* and for dysentery bacilli gave negative results; an abundance of pyocyanus bacilli was found. Camphorated tincture of opium and acetyltannic acid and later acidophilus milk were given by mouth. Rectal irrigations of silver nitrate, 1:3,000, and plain water were also

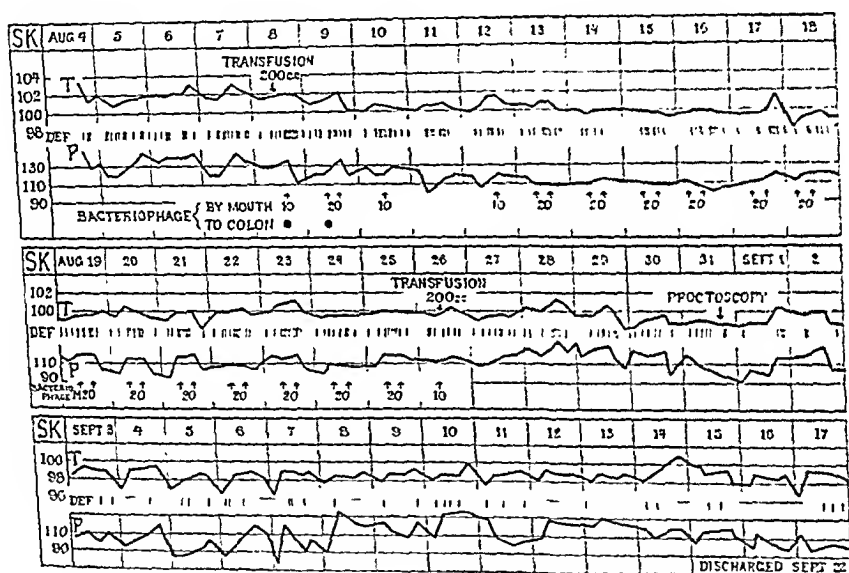


Chart 1 (case 3).—The course of the temperature (T), pulse rate (P) and number of stools (DEF) each day, and the amount and time of administration of bacteriophage and transfusions of blood.

administered. Uncontrolled diarrhea continued with from four to thirty liquid stools a day, and the patient continued to lose strength and weight. Sores from pressure were present on the buttocks. On December 27 the patient was delirious and defecation was involuntary. On December 28 abdominal distention and edema of the lower extremities were noted. A transfusion of blood given at 4 p. m., on December 29 was followed at 4:45 p. m. by a chill which continued to 5:35 p. m. On December 30 the patient was moribund. She was delirious and passed five involuntary stools during the following night. On the morning of December 31 the pulse rate was stronger.

A mixed bacteriophage potent against colon bacilli, dysentery bacilli, staphylococci and some varieties of streptococci was made up on December 30 and was given to the patient by mouth on December 31 at 3 p. m. and again at 10 p. m.

1. Dr. Warren provided the record of the course of this patient.



taining the proteus bacteriophage.<sup>2</sup> Clinical notes on January 13, 14 and 15 and subsequent days record continued improvement in the general clinical condition and in the character of the stools. The amount of food was increased. Transfusions on December 29 and January 3 and 9 were followed in each instance by a chill. Chills also followed the later transfusions on February 5, 13 and 17.

Apparently there was a complicating infection of the upper respiratory tract about January 26.

Gain in strength was very slow. The frequency of defecation continued, but the stools became less liquid and of smaller volume. A culture of colon bacilli was introduced into the rectum on March 2 and March 3. The patient was discharged from the hospital on March 27, 1931. In a letter dated June 6, 1931, the patient reported that she felt well and had a good appetite, but still had trouble with her bowels, "expelling gas and squirts during the day as many as eight times, but at night maybe once or twice."

#### PATIENTS WITH INTESTINAL FISTULA

In conjunction with these cases of chronic colitis it seems proper to present the summarized records of two patients, in each of whom a fecal fistula developed following difficult surgical treatment of a complicated disease of the pelvis. In each of these the use of bacteriophages seems to have been one factor in changing an apparently progressive downward postoperative course into a rather discouraging state characterized by lack of progress in either direction, which was finally transformed into slow improvement and eventual restoration to health. The complete hospital records of these patients are available, and exemplify the behavior of patients suffering from mixed infection with intestinal bacteria when treated with bacteriophage.

CASE 5.—J. F., a white woman, aged 44, was admitted on July 19, 1931, to the service of Dr. John F. Erdmann. In 1916, after a repair of the perineum and suspension of the uterus, the patient had been informed that she had a tumor in the pelvis situated between the rectum and the spinal column. This caused no discomfort and was neglected until May, 1930, when, following a cold, there was retention of urine requiring catheterization. From July to October, 1930, the patient received some roentgen treatment. On July 21, 1931, a laparotomy was performed which lasted ninety minutes. Included in the operation were subtotal hysterectomy, bilateral salpingo-oophorectomy, removal of a partly disintegrated tumor posterior to the rectum and involving the left ureter, implantation of the left ureter into the bladder at a new site and incision between the coccyx and the anus for the removal of part of the disintegrating tumor mass and for drainage of the pelvic cavity. There were multiple fibroids of the uterus. The disintegrating tumor in the back of the pelvis was regarded at the time of the operation as a malignant process. Subsequent study in the laboratory failed to disclose evidence of malignancy. The growth appeared to be a partly necrotic cystic mass of unusual character.

The postoperative course was stormy. There was blood in the urine on July 22, and frequent vomiting occurred. On July 30 there was a foul odor from the

2. This note was made by Dr. Warren. It does not check exactly with the record on the chart, but the latter may be erroneous.

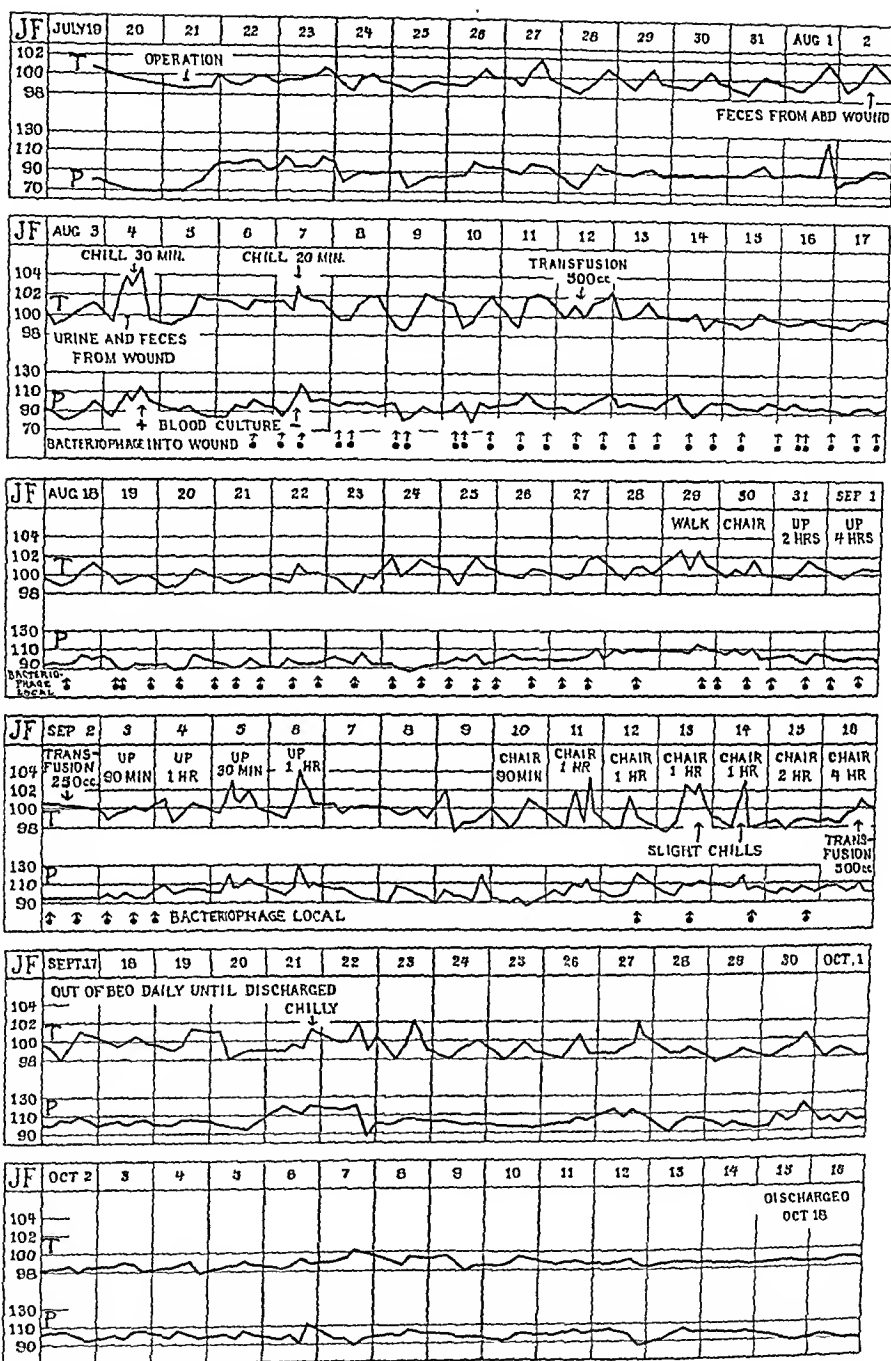


Chart 3 (case 5).—The course, including temperature and pulse rate, and the administration of bacteriophage.

abdominal wound, and on August 2 fecal material was recognized on the dressing of the wound. On August 4 both urine and feces were recognized coming from the abdominal wound. On this day there was a chill lasting thirty minutes and a rise of temperature to 104.4 F. A blood culture taken at this time gave a growth of a paracolon bacillus, type undetermined. Cultures from the abdominal wound on August 5 revealed mixed infection. The dominant organisms in the plate cultures were colon bacilli of the lactic acid variety, staphylococci and paracolon bacilli. It was possible to find potent bacteriophages for the colon bacillus and the staphylococcus, but not for the paracolon bacillus.

On August 6 a broth-bacteriophage mixture active against the colon bacillus and the staphylococcus was introduced into the abdominal wound and once, twice or three times a day thereafter until September 4. On August 7 there was a chill lasting for twenty minutes. A blood culture taken at this time remained negative. Transfusions of blood were given: 500 cc. on August 12 and 250 cc. on September 2. Cultures of the urine on August 21 revealed colon bacilli of the lactic acid variety, staphylococci and paracolon bacilli in abundance. The paracolon bacillus was evidently playing an important rôle. Unfortunately we were unable to find a bacteriophage potent against it. Cultures from the wound on September 1 yielded a colon bacillus of the lactic acid variety and *Bacillus pyocyaneus*. Neither of these was susceptible to bacteriophage races in the laboratory. Another culture from the wound on September 11 yielded *Escherichia acidilactici*, resistant to our bacteriophage races, and an enterococcus in the broth culture. In spite of these unpromising laboratory findings, the mixed bacteriophage was again applied to the abdominal wound daily from September 12 to September 15. On September 16 a transfusion of 500 cc. of blood was given. The patient was now out of bed daily until discharged on October 18.

In this patient the fistulous tract apparently communicated with both the intestines and the bladder. Urine was observed on the abdominal dressing repeatedly from July 31 to September 28, and fecal material from August 2 to September 26. After September 28 neither of these was again recognized on the dressing.

CASE 6.—C. H., a white woman, aged 34, a patient of Dr. Eilif C. Hanssen, was admitted on June 29, 1931. Colpotomy was performed on July 1, the incision opening into a large pelvic abscess. Bacteriologic examination of the pus from this abscess revealed *Streptococcus viridans* and a gram-positive anaerobic bacillus, not further identified. After improvement for two or three days the clinical condition again became unsatisfactory, and on July 6 there was a chill lasting for twenty minutes, with a rise of temperature to 106.2 F. A blood culture taken at this time remained negative. *Streptococcus serum*, 30 cc., was given on the evening of July 6 and a transfusion of 500 cc. on July 7.

On July 10 the abdomen was opened by incision in the midline, and an infected papillary cyst of the right ovary was aspirated and partly removed. Because of dense adhesions, part of the wall of the cyst was not excised. Drainage was established through the abdominal wall as well as through the vaginal vault. Bacteriologic study of the contents of the cyst revealed colon bacilli of the lactis-aerogenes type and a few hemolytic streptococci. Histologic study of the cyst wall showed it to be an ovarian papillary cystadenoma. Following the operation a transfusion of 500 cc. of blood was given. The postoperative course was fairly satisfactory until July 14, when part of an enema being given by the nurse escaped through the abdominal incision, and on changing the dressings a large amount of fecal material was found in the wound and on the dressing. A blood culture taken on July 15 remained negative. A transfusion of 500 cc. of blood was given on

July 20. Urticaria appearing on July 21 and 22 may have been related to the dose of streptococcus serum given on July 6, although fifteen days had elapsed.

Bacteriophages were employed for the first time on July 25. On this day a specimen of exudate from the abdominal fistula was taken for bacteriologic study, and then, without awaiting the results of this examination, a broth mixture of stock bacteriophages potent against the colon bacillus, staphylococcus and streptococcus and *B. pyocyaneus* was employed to irrigate the sinus. On July 26 the

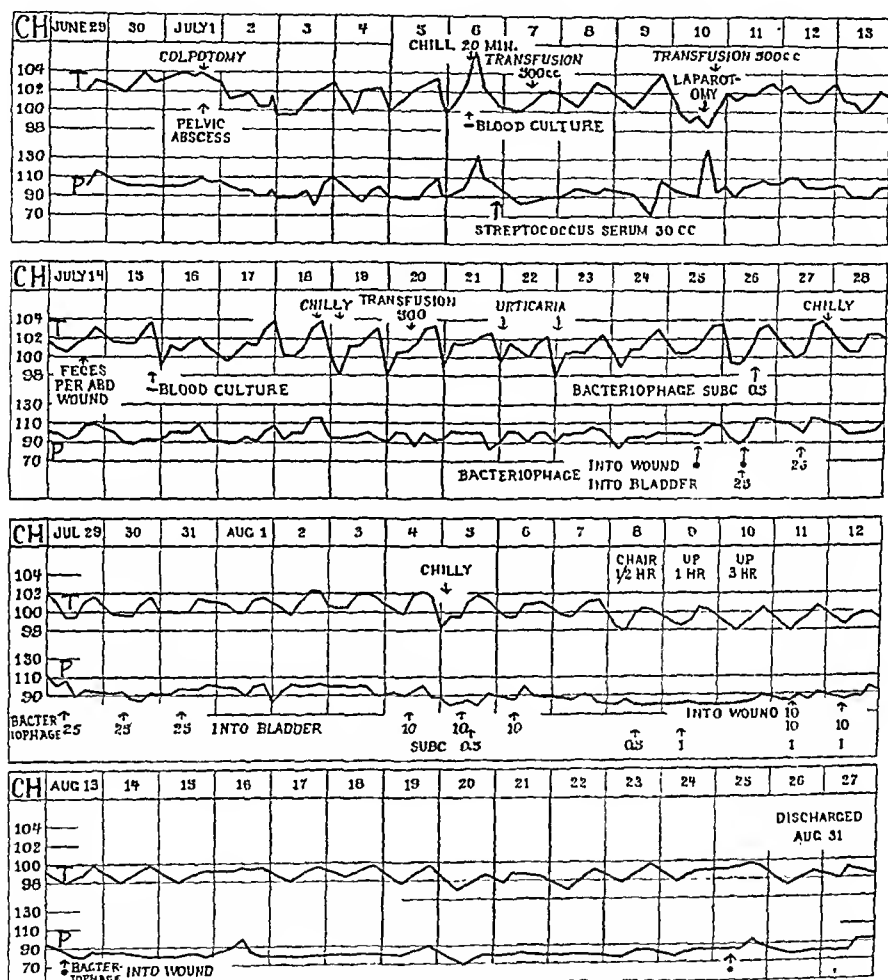


Chart 4 (case 6).—The course, including temperature and pulse rate, and the administration of bacteriophage.

fistulous tract was again irrigated with the same bacteriophage mixture, and 25 cc. of it was introduced into the bladder by a catheter and left there. On July 27 the fistulous tract was irrigated with 25 cc. of the bacteriophage mixture, and the mixture was introduced into the bladder in amounts of 25 cc. on July 29, 30 and 31. A subcutaneous dose of 0.5 cc. of the broth-bacteriophage preparation was given on July 26. There was a slight febrile reaction, apparently related to the subcutaneous injection. By July 29 there was distinct evidence of improvement in temperature, pulse rate and clinical condition.

The specimen of exudate from the fistula obtained on July 25 gave abundant growth of colon bacilli, among which the lactic acid variety was predominant. A specimen of urine obtained from the bladder on July 26, previous to the intravesical bacteriophage treatment, contained many pus cells, and the cultures yielded colon bacilli of the communis variety. A potent specific bacteriophage against this organism was prepared by serial filtration.

The administration of potassium citrate by mouth had been started on July 25, and the dose of this agent was adjusted so as to keep the urine nearly neutral in reaction. Red and blue litmus paper, phenolsulphonphthalein and bromocresol purple, with suitable comparators, were employed to test the reaction of the urine.

On August 4 the use of the newly prepared bacteriophage specific for the colon bacillus in the bladder was initiated. Five instillations of 10 cc. of the preparation were given into the bladder on August 4, 5, 6, 11 and 12, respectively. Five subcutaneous injections of the same preparation were also given: a dose of 0.5 cc. on August 5 and again on August 8 and doses of 1 cc. each on August 9, 11 and 12. The bacteriophage preparation of mixed stock was employed to irrigate the fistulous tract on August 11 and 13 and again on August 25.

Bacterial counts on urine from the bladder showed 276,000,000 per cubic centimeter on August 5, 7,400,000 on August 6, 162,000,000 on August 11, 72,000,000 on August 12 and 327,500,000 on August 24. The predominating organism in the last specimen was a colon bacillus of the lactic acid variety which was only partially susceptible to the bacteriophage used.

The clinical course was that of gradual improvement. Fecal material was recognized on the dressings of the abdominal wound on August 4 for the last time. After August 12 the temperature was always below 100 F. until the patient was discharged on August 31. The sinus in the abdominal wall was still secreting a small amount of exudate on August 31. On Oct. 21, 1931, she was seen by Dr. Hanssen. She had gained 20 pounds (9.1 Kg.) and the sinus was almost healed. On May 11, 1933, in response to a follow-up inquiry, she reported herself as well and steadily at work. The physician in attendance and those who saw this patient in consultation have expressed conviction that the bacteriophage therapy was of distinct service in this case.

#### COMMENT

In the introductory paragraphs we expressed some diffidence about presenting the records of these patients, because it seemed to us that a claim of a favorable effect of treatment by bacteriophage in these cases rests on evidence distinctly less convincing when compared with the observations on septicemia and on infections of the urinary tract. The problem of mixed infections presents complex difficulties to the bacteriologist who has been trained to a wholesome skepticism based on the postulates of Henle and of Koch.

The apparent favorable influence of the preparations of bacteriophage in these patients may have resulted: (1) from an actual destructive and restraining influence on the infecting microbe; (2) from a psychic encouragement of the patient who may be emotionally influenced by the thought of a mysterious agent which is capable of seeking out and opposing his microbic enemies, or (3) from a stimulus to more precise and more enthusiastic general clinical care by the physician because a



problematic and interesting new therapeutic agent had been made available. We are inclined to think that all three of these factors may play a part in the ultimate outcome of a case. Especially important is the enthusiasm of the clinician who is actually at the bedside. If he is not interested and does not welcome the aid of the bacteriophages it is easily possible to fail in the treatment.

As far as we have observed, the use of preparations of bacteriophage by mouth or by injection into fistulous tracts is without untoward effects. On the other hand, there is some evidence to indicate an irritant effect when these are introduced through a colonic tube into the inflamed intestine, and there is convincing proof that local irritation and a general rise in temperature may follow subcutaneous or intramuscular injection. In the group of cases reported in this paper serious untoward effects which could be ascribed to the use of the bacteriophages were not observed.

#### SUMMARY

The empirical use of preparations of bacteriophage potent against some of the intestinal microbes has been followed by favorable results in patients suffering from chronic colitis of undetermined causation. Because of the evident harmless nature of this therapy, it would appear worthy of trial in this sometimes baffling condition. Postoperative intestinal fistulas infected with a mixture of intestinal bacteria have been, in two instances, favorably influenced by the use of bacteriophages active against the intestinal bacteria.

The therapeutic results are not dramatic. The bacteriophages seem rather to exercise a merely beneficent influence on the course of the essentially chronic ailment.

# EFFECT OF EPINEPHRINE ON THE SYMPATHECTOMIZED HUMAN EXTREMITY

AN ADDITIONAL CAUSE OF FAILURE OF OPERATIONS FOR  
RAYNAUD'S DISEASE

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We have recently observed a recurrence of vascular spasm after complete sympathectomy in a number of cases of Raynaud's disease; in two instances the recurrence appeared within two weeks after the operation. In 1905 Elliott<sup>1</sup> showed that in animals structures innervated by the sympathetic nervous system become sensitized to epinephrine after denervation, and the theory was recently emphasized by Rosenblueth and Cannon.<sup>2</sup> We have carried out a series of experiments on human beings and on animals, the results of which are given in this communication and which we believe show that recurrence of vascular spasm after complete sympathectomy, in man as well as in animals, is probably due to sensitization of the sympathectomized extremities to epinephrine.

Sympathetic ganglionectomy for vascular disease of the extremities has been performed in seventy-five cases by the members of the clinic for circulatory diseases of the Massachusetts General Hospital. The great majority of these operations have been performed for vascular spasm, although we have operated on a few patients with underlying obliterative vascular disease in whom the element of vascular spasm was striking.

The immediate results have been very satisfactory,<sup>3</sup> but the same cannot be said of the end-results.<sup>4</sup> We have found the beneficial effect

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From the surgical services of the Massachusetts General Hospital.

Dr. Bradford Cannon and Dr. Henry Heyl assisted in carrying out the tests in a number of the cases studied.

1. Elliott, T. R.: The Action of Adrenalin, *J. Physiol.* **32**:401, 1905.

2. Rosenblueth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Glands; Some Effects of Sympathin on the Nictitating Membrane, *Am. J. Physiol.* **99**:398 (Jan.) 1932.

3. (a) White, J. C.: Experiences with Sympathetic Ganglionectomy in Peripheral Circulatory Disease, *New England J. Med.* **204**:852 (April 23) 1931; (b) Raynaud's Disease: Studies on Post-Operative Cases Bearing on the Efficiency of Sympathetic Ganglionectomy, *ibid.* **206**:1198 (June 9) 1932.

4. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thromboangiitis Obliterans by Desensitization of Peripheral Sensory Nerves, *Ann. Surg.* **96**:867 (Nov.) 1932.

of lumbar ganglionectomy to be more permanent than that of dorsal ganglionectomy. To eliminate vascular spasm in the vessels of the lower extremity, we have attempted to remove the lumbar trunk from above the second to below the fourth lumbar ganglion. In the majority of instances, we have removed a portion of the chain which included three ganglions, probably the second, third and fourth lumbar.

At first we believed in common with others that to sympathectomize the upper extremity it was sufficient to remove the first and second or even the second and third dorsal ganglions. The immediate results seemed equally satisfactory, but in the course of from six months to a year, a recurrence of varying degrees of vascular spasm was frequently observed. We believed that this was either because efferent vasoconstrictor impulses were reaching the vessels through pathways which had not been interrupted, or because regeneration of nerve fibers occurred. In a number of these cases further surgical intervention has been resorted to when it was possible to demonstrate by paravertebral procaine hydrochloride block or by other methods that there remained a definite connection between the cervicodorsal sympathetic ganglions and the cords of the brachial plexus. After this connection had been interrupted, there followed a striking rise in peripheral surface temperature and other evidence of a complete sympathectomy in the extremity. As a result of these secondary operations, we have arrived at the belief that in order to sympathectomize the upper extremity it is necessary to remove the sympathetic chain from above the inferior cervical ganglion to below the second dorsal ganglion. This technic has been followed in all our cases during the past year and has recently been reported in another communication.<sup>5</sup>

Following this more complete operation, we have repeatedly noticed the reappearance of vascular spasm at varying intervals. In some patients spasm could be produced by exposure to cold, in response to pain and following emotional stimuli. Another patient was symptom-free for nine months after sympathectomy of both upper extremities, and then vascular spasm developed which resulted in mild gangrene of the tips of two fingers of each hand during the tenth month (fig. 1). This patient's history revealed that during that month she had been caring for a sick relative and had been much upset emotionally. Furthermore, the original appearance of vascular spasm dated from the sudden death of her husband nearly five years previously.

These patients, as well as others, have been put through exhaustive tests<sup>3b</sup> which, we believe, have demonstrated that there has been a com-

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5. White, J. C.; Smithwick, R. H.; Mixter, W. J., and Allen, A. W.: A New Muscle Splitting Incision for Resection of the Upper Thoracic Sympathetic Ganglia, *Surg., Gynec. & Obst.* 56:651 (March) 1933.

plete interruption of the efferent sympathetic pathways to the extremities in question; this tends to prove that the recurrence of vascular spasm cannot be explained on the basis of either an incomplete surgical procedure or regeneration of nerves. Progress of local disease might be offered as an explanation, but obviously the time element makes this solution highly improbable. The close association of the recurrent spasm with emotional stimuli followed by periods of almost total absence of spasm strongly suggested the direct action on the blood vessels of the circulating hormone, epinephrine. That some patients are able to secrete sufficient epinephrine into the blood stream to produce vasospasm in the sympathectomized area is, we believe, shown by the following experiments.



Fig. 1 (case 2, B. R.).—Gangrene of tips of two fingers of each hand ten months after ganglionectomy. Gangrene appeared during the tenth month while the patient was under prolonged emotional strain. Previous to this the patient had been symptom-free. In this instance the gangrene is presumably caused by vascular spasm in the sensitized areas due to increased secretion of epinephrine in response to emotion.

Nine patients (listed in the table) from our total series have been studied to determine whether their sympathectomized extremities are sensitized to epinephrine. In each instance it has first been shown by procaine hydrochloride block and by other tests whether or not the extremities in question have been completely sympathectomized. The response to epinephrine (figs. 2 and 3) has then been determined by the prolonged intravenous administration of a solution of epinephrine chloride in physiologic solution of sodium chloride in a 1:250,000 dilution, at the rate of from 40 to 60 drops a minute, after first establishing the response to physiologic solution of sodium chloride given intravenously at the same rate and under the same conditions.

# Sensitization of Sympathectomized Extremities to Epinephrine

Case	Sex	Age	Diagnosis	Operation	Time Since Operation	Degree of Vascular Spasm Following:		Clinical Recurrent Spasm
						Epinephrine 1:250,000	Insulin	
1. L. M.	F	39	Vasomotor spasm with early peripheral arteriosclerosis	Bilateral cervicodorsal ganglionectomy Bilateral lumbar ganglionectomy	22 days	Marked	Marked	Marked
2. B. R.	F	44	Raynaud's disease with scleroderma	Bilateral cervicodorsal ganglionectomy	10 months	Marked	Marked	Marked
3. F. MeV.	M	32	Raynaud's disease	Right cervicodorsal ganglionectomy	10 days	Marked	Not done	Marked
4. P. B.	F	27	Raynaud's disease	Right dorsal (first and second) ganglionectomy; incomplete operation	3 years	None	None	Marked
5. P. R.	F	20	Vasomotor instability	Bilateral lumbar ganglionectomy	5 months	Moderate	Moderate	None
6. R. F.	F	19	Idiopathic epilepsy	Bilateral cervicodorsal ganglionectomy	12 days	Not done	Marked	.....
7. S. T.	M	41	Bronchial asthma	Left cervicodorsal ganglionectomy	15 months	Moderate	Moderate	.....
8. M. MeG.	F	21	Raynaud's disease	Right cervicodorsal ganglionectomy	3 months	Marked	Not done	None
9. R. U.	M	44	Bronchial asthma	Paravertebral injection of alcohol (first, second and third dorsal); marked Horner's syndrome	2 days 6 days 8 days 18 days	None None Mild Moderate	Not done	.....

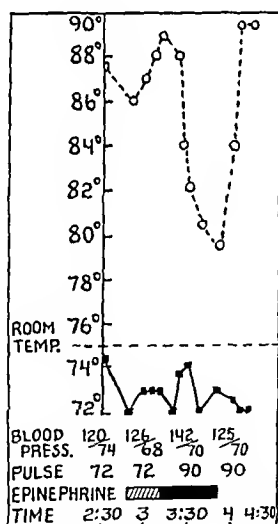


Figure 2

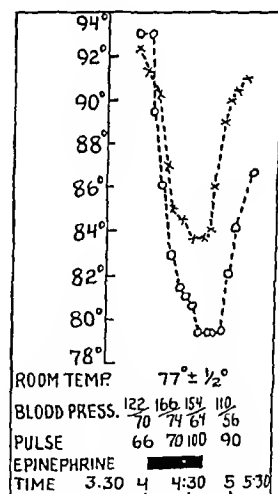


Figure 3

Fig. 2 (case 8, A. McG.).—Raynaud's disease. Typical response to intravenous injection of epinephrine three and one-half months after cervicodorsal ganglionectomy. This chart shows the degree of vascular spasm in the sympathectomized extremity as contrasted with the absence of vascular spasm in the normally innervated extremity. The circles and dotted line indicate the temperature for the denervated third finger of the right hand; the blocks and solid line, the temperature of the normally innervated third toe of the right foot.

Fig. 3 (case 1, L. M.).—Raynaud's disease. The test performed ten weeks after cervicodorsal and three weeks after lumbar ganglionectomy shows a typical response to intravenous administration of epinephrine. Note the degree of vascular spasm in both upper and lower extremities. The circles and dotted line indicate the temperature in the denervated third finger; the crosses and dotted line, the temperature in the denervated third toe.

In view of the fact that hypoglycemia has been shown to stimulate the secretion of epinephrine in animals,<sup>6</sup> it seemed fair to expect a similar reaction in human beings. The concentration of epinephrine in the circulating blood would presumably be temporarily increased and should therefore be accompanied by vascular spasm in the sympathectomized area. This should result in a fall in surface temperature, which was found to occur in every instance. A typical reaction of a sympathectomized extremity during hypoglycemia is represented in figure 4.

The acutely sympathectomized extremity (procaine hydrochloride block) reacts as does a normally innervated extremity (fig. 5); hence

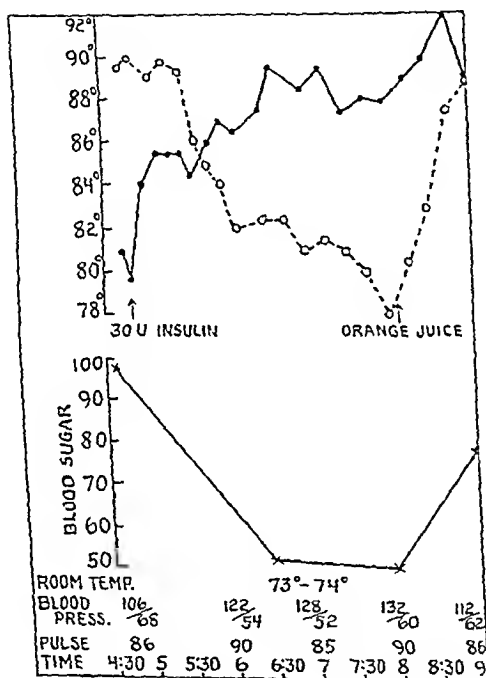


Fig. 4 (case 6, R. F.).—Typical reaction to secretion of epinephrine in insulin hypoglycemia twelve days after a left cervicodorsal ganglionectomy. Note the vascular spasm in the sympathectomized extremity and the absence of spasm in the normal extremity; in fact, the temperature of the normal extremity rose during the experiment. The spasm in the sympathectomized extremity is similar to that shown in figures 2 and 3, but the fall in temperature is more gradual, perhaps because the rise in the amount of epinephrine in the blood is presumably more gradual in response to hypoglycemia than when the substance is injected directly into the blood stream. The open circles and dotted line indicate the temperature in the denervated third finger of the left hand; the solid circles and solid line, the temperature in the normal third finger of the right hand.

6. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am. J. Physiol.* **69**: 46 (June) 1924.

it is impossible to predict which patients will have a clinical recurrence of vascular spasm after operation. Figure 5 also illustrates the fact that the incompletely sympathectomized extremity is not sensitized to epinephrine. In this instance (table, case 4) a dorsal ganglionectomy had been performed three years previously in an attempt to sympathectomize an upper extremity for Raynaud's disease. At that time the first and second dorsal ganglions, the intervening trunk and all communicating rami over this extent had been removed. There followed a clinical recurrence of vascular spasm about one year after operation. We believe that this test enables us to prove whether or not an extremity is completely sympathectomized.

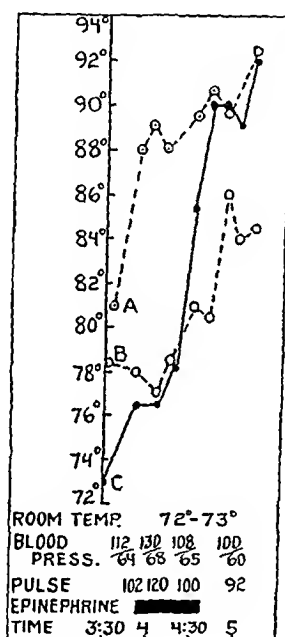


Fig. 5 (case 4, P. B.).—Raynaud's disease. *A*, temperature of the third finger following incomplete sympathectomy of the right arm with reestablishment of vasomotor tone. *B*, temperature following acute denervation of the little finger of the left hand following injection of procaine hydrochloride into the ulnar nerve. *C*, temperature of the normal third finger of the left hand. The right hand, with reestablishment of its sympathetic connections, shows no sensitivity to epinephrine. The acutely denervated finger, in which the sympathetic nerves are paralyzed but have not degenerated, shows complete vasodilatation, but no evidence of sensitization to epinephrine.

At the present time, a series of experiments with animals is in progress to support our clinical data. The results so far are entirely in agreement with those noted in man. It has also been shown in cats and in rabbits that when the right suprarenal gland has been denervated and the left resected, vasospasm in the sympathectomized extremity or

denervated ear which had previously been present during insulin hypoglycemia, was entirely eliminated. These data will be reported in full in another communication.<sup>7</sup>

#### COMMENT

During the intravenous administration of epinephrine chloride (figs. 2 and 3) in high dilution, 1:250,000, there is a rapid fall in the surface temperature of the sympathectomized extremity. At the same time, the color of the extremity becomes definitely cyanotic, particularly in cases in which some organic obstruction is present in the peripheral vessels. When the administration of epinephrine ceases there is a marked rise in surface temperature of the extremity, and the color becomes normal. The normally innervated extremity shows comparatively little change in surface temperature or color. Following procaine hydrochloride block the acutely sympathectomized extremity does not appear to be sensitized and reacts essentially as does the normally innervated extremity (figs. 2 and 5). The incompletely sympathectomized extremity (fig. 5) also reacts as does a normally innervated extremity.

Insulin hypoglycemia (fig. 4) produces a fall in the surface temperature of the sympathectomized extremity which is similar to that which has been shown to occur with the injection of epinephrine. We have interpreted this as further evidence to support the theory of Cannon, McIver and Bliss<sup>6</sup> that there is hypersecretion of epinephrine into the blood stream in this state. As far as the problem at hand is concerned, we believe that the reaction of the sympathectomized extremity to epinephrine administered intravenously and to insulin hypoglycemia is similar. This suggests that the vascular spasm which accompanies hypoglycemia is due to increased secretion of epinephrine into the patient's blood stream.

We believe that the completely sympathectomized extremity becomes sensitized to epinephrine chloride circulating in the blood stream between seven and eight days after operation (fig. 6).

From a clinical point of view, it is impossible as yet to state the full significance of these findings. It is distressing, to say the least, to find a recurrence of vascular spasm within two weeks after an extremity has been completely sympathectomized. We are not aware of the clinical return of vascular spasm as soon as this after what we now term an incomplete operation. In the earlier cases, recurrence of symptoms in from six months to a year was a frequent occurrence. Whether vascular spasm due to the direct action of epinephrine on the blood vessels after sympathectomy will cause as severe symptoms and

7. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man, The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia. *Am. J. Physiol.* **107:3** (March) 1934.



as marked circulatory insufficiency as the original disease (spasm due to efferent sympathetic impulses) remains to be seen. We know that it can produce gangrene of the tips of two fingers of each hand (fig. 1). Although we believe that all sympathectomized extremities will be sensitized to epinephrine injected intravenously, we do not believe that every patient will show a clinical return of spasm after an apparently complete operation. Two patients (table, cases 5 and 8) are completely sympathectomized, sensitized to epinephrine, but clinically cured. In cases 1, 2 and 3 there is marked clinical spasm, although in case 1 this spasm is much more noticeable in the upper than in the lower extremities.

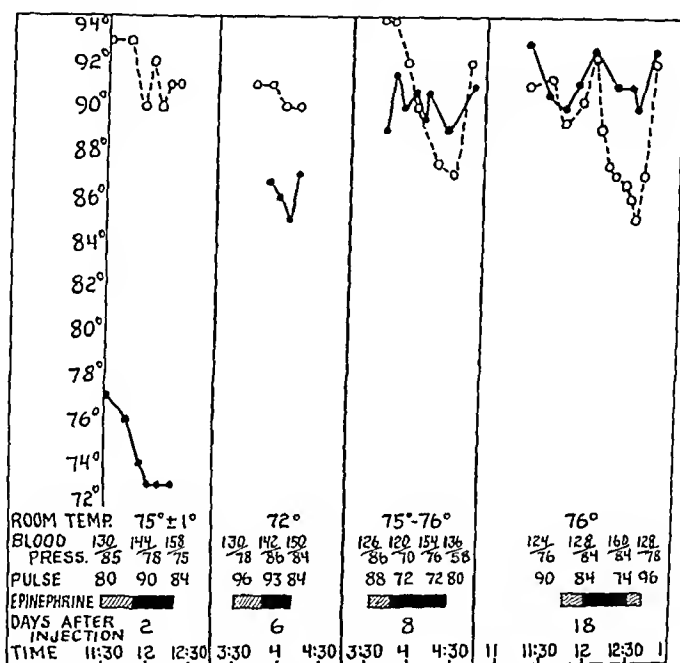


Fig. 6 (case 9, R. U.).—Complete paralysis of the cervicodorsal sympathetic nerves after injection of alcohol for bronchial asthma. These charts illustrate the development of sensitization to circulating epinephrine. Sensitization of the arteries appears between the seventh and eighth days after the injection and is complete by the eighteenth day. The open circles and dotted line indicate the temperature of the denervated fifth finger of the left hand; the solid circles and solid line, the temperature of the normal fifth finger of the right hand.

This spasm appears particularly in response to cold, but also in response to pain and emotional stimuli. The cold threshold seems to be slightly higher than it was before operation, and in general the spasm is less intense and more readily relieved by immersion of the extremities in warm water. This suggests that as far as possible the after-care of these patients should aim toward the production of a state of emotional stability. Freedom from worry and attempts to adjust psychologic problems are undoubtedly important.

From a surgical point of view, complete excision of the medullary portion of the suprarenal glands, sympathectomy of both suprarenal glands or sympathectomy of one and excision of the other may offer a solution. We have performed the latter operation in rabbits and cats in order to prove that the influence of the suprarenal glands on the sympathetomized extremity can be eliminated. Whether this will be followed by some untoward effect on the animals or whether they will be able to lead a comparatively normal life after such an operation can be told only after sufficient time has elapsed. It is possible that the sympathetic nerve supply to the remaining suprarenal gland will regenerate, and it is possible that the liver or some other organ can produce an internal secretion to take the place of epinephrine. In either case the vascular spasm may recur.

#### SUMMARY AND CONCLUSIONS

1. The fact that in animals structures innervated by the sympathetic nervous system become sensitized to circulating epinephrine following sympathectomy has been shown by Elliott as well as by Rosenbluth and Cannon. Evidence is presented in this report that human blood vessels become sensitized to epinephrine in the same manner following resection of sympathetic ganglions.

2. Tests in a series of nine cases in man following complete sympathetic denervation of extremities have shown marked vasospasm in the presence of minute quantities of epinephrine in the circulating blood. Thus the intravenous infusion of a 1:250,000 solution of epinephrine, an amount which causes little change in the normal extremity, is sufficient to lower the surface temperature of the denervated side as much as 15 F. Similar changes take place when the patient's suprarenal glands are stimulated to secrete epinephrine by insulin hypoglycemia.

3. Identical vasospastic phenomena, which occur in sympathetomized cats and rabbits in insulin hypoglycemia, are abolished by suprarenal denervation.

4. This hypersensitization of the arteries to epinephrine takes place only on degeneration of the vasomotor nerves. It is not present after procaine hydrochloride block or during the first week after operation. We have found that it takes from seven to eight days for sensitization to appear.

5. We believe that this hypersensitivity to the circulating hormone, epinephrine, which develops in sympathetomized extremities, constitutes a hitherto unrecognized but important source of unsatisfactory results in Raynaud's disease.

# STRUMA LYMPHOMATOSA (HASHIMOTO) ASSO- CIATED WITH HYPERTHYROIDISM

REPORT OF A CASE WITH CLINICAL AND HISTOPATHOLOGIC STUDY

DAVID POLOWE, M.D.

PATERSON, N. J.

The case of struma lymphomatosa which is the subject of this report derives its importance from the fact that it was associated with hyperthyroidism in a young woman. The few cases thus far reported have in common the facts that the pathologic entity was found in women over 40, and that it was associated with no thyroid symptoms other than those that might be ascribed to moderate compression of the trachea. Some authors have observed hypothyroidism and myxedema as late effects. A few authors have felt that one could not exclude hyperthyroidism as an insidious precursor to the disease. As far as I can discover, this is the first case to be reported of struma lymphomatosa associated with hyperthyroidism. As such it furnishes an interesting link, perhaps the first stage in the pathogenesis of the obscure thyroid disease known as the struma lymphomatosa of Hashimoto<sup>1</sup> or the lymphadenoid goiter of Williamson, Scott and Pearse.<sup>2</sup> Thus, evidence is now at hand to show that clinically the reconstructed sequence of events may be: first, a phase of hyperthyroidism; second, a phase of apparently normal thyroid activity which may or may not be associated with symptoms referable to compression of the trachea, and, third, a hypothyroid or myxedematous phase which, also, may or may not be associated with symptoms referable to compression of the trachea. Because of its usually insidious course it is conceivable that struma lymphomatosa may go unnoticed in any of its phases during the life of the patient. The rarity of the condition and the distinctive pathologic process found are sufficient apology for basing this report on one case.

## REVIEW OF THE LITERATURE

Struma lymphomatosa was first described by Hashimoto,<sup>1</sup> in 1912. He reported four cases. Williamson, Scott and Pearse,<sup>3</sup> in 1925, while examining two thousand specimens of thyroid tissue for the purpose of classifying them on a pathologic basis, found some glands (the exact

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1. Hashimoto, H.: Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma Lymphomatosa), Arch. f. klin. Chir. **97**:219, 1912.

2. Williamson, G.; Scott, G., and Pearse, I. H.: Lymphadenoid Goitre and Its Clinical Significance, Brit. M. J. **1**:4, 1929.

3. Williamson, G.; Scott, G., and Pearse, I. H.: The Pathological Classification of Goitre, J. Path. & Bact. **28**:361, 1925.

number was not stated) with the distinctive pathologic changes which they termed lymphadenoid goiter. They described the pathologic change in much greater detail in 1929.<sup>2</sup> Ewing,<sup>4</sup> in 1928, stated that he saw four cases of the Hashimoto type, but believed them to be early stages of Riedel's struma, which Riedel reported in 1896. But in his report Riedel made no mention of the extensive infiltration of the gland with lymphocytes and lymph follicles. Joll,<sup>5</sup> in his short chapter on lymphadenoid goiter, gave plausible reasons for considering Riedel's struma an entirely different disease entity from struma lymphomatosa. Graham and McCullagh,<sup>6</sup> in 1931, reported four cases of the Hashimoto type.

#### ETIOLOGY

The etiology of struma lymphomatosa is obscure. McCarrison,<sup>7</sup> in 1929, produced a condition simulating lymphadenoid goiter. He used rats, and fed them American white flour, meat residue, olive oil and table salt containing a little potassium iodide. It required a few months on this diet to produce the condition. He concluded that deficiency of iodine is not a factor in the production of lymphadenoid goiter, and that deficiency of vitamins is a factor.

#### PATHOGENESIS

In considering the pathogenesis of struma lymphomatosa it is well to bear in mind the two functions of the thyroid gland: (a) the lymphogenic process, the secretion of which does not contain thyroxine and (b) the colloid-producing function, in which the colloid contains thyroxine. In struma lymphomatosa, undue strain falls on the lymphogenic process. The replacement fibrosis which occurs, though constant in the later stages, is never the most conspicuous feature of the histologic change. Williamson and his associates describe it with great accuracy as follows:

The lymphocytic infiltration is peculiar in that it picks out specific thyroid lymph spaces in a most delicately selective fashion. As the disease progresses the lymphogenesis becomes more and more active; lymphocytes begin to collect at the hilum of the gland unit and to arrange themselves in a circular fashion around its circumference as they crowd in the perivascular lymph spaces about the capsule

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4. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 961.

5. Joll, Cecil A.: *Diseases of the Thyroid Gland*, St. Louis, C. V. Mosby Company, 1932, p. 112.

6. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid: Struma Lymphomatosis (Hashimoto), *Arch. Surg.* 22:548 (April) 1931.

7. McCarrison, R.: Note on the Experimental Production of Lymphadenoid Goitre in Rats. *Brit. M. J.* 1:5, 1929.

of the gland units. The parenchyma, which produces the lymphogenic secretion, becomes hyperplastic, and active mitosis appears in the epithelium. As the process advances, abnormal lymphogenic activity claims the whole field, and colloid storage becomes inconsiderable. Exhaustion of the epithelium eventually ensues, and now, no longer able to produce secretion, becomes atrophic.

#### DIAGNOSIS

Clinical recognition of struma lymphomatosa is impossible in the presence of hyperthyroidism, which I consider the earliest stage of the disease. In the later stages the following criteria may help in making a preoperative diagnosis (Graham and McCullagh<sup>6</sup>): 1. There is uniform bilateral firm or hard enlargement of the thyroid gland without notable deformity of the lobes and without definite nodules. 2. There is close attachment of the thyroid gland to the trachea without adherence to overlying structures. 3. It occurs in women in middle life or over. 4. There are no symptoms other than those that might be ascribed to moderate compression of the trachea. 5. There is no impairment of the general health. 6. There is no involvement of regional lymph nodes or evidence of distant metastases. 7. There are no signs of local inflammation.

Joll<sup>5</sup> stated his objections to classifying struma lymphomatosa as an early stage of Riedel's struma as follows: 1. Struma lymphomatosa is confined almost entirely to women over the age of 45. Riedel's struma may appear at any age, and men are affected nearly as often as women. 2. Struma lymphomatosa tends to the development, sooner or later, of myxedema. Riedel's struma rarely leads to hypothyroidism, even after extensive resection of the thyroid gland. 3. Struma lymphomatosa is a diffuse process at the start, no part of the gland escaping. In Riedel's struma, localization to a lobe or part of a lobe is usual. 4. Widespread formation of delicate connective tissue is characteristics of struma lymphomatosa in the advanced stages. Dense fibrosis, comparable to scar tissue, is found in the earliest stages of Riedel's struma. 5. In struma lymphomatosa there is no involvement of the surrounding structures. In Riedel's struma such involvement is characteristic.

#### REPORT OF A CASE

Miss H. E., aged 26, white, presented herself for examination on July 14, 1933. Her chief complaint was that her doctor told her that she had high blood pressure. She had gone to him with the chief complaint that for the past eighteen months she perspired so profusely that she had to change her clothing several times a day, that she was constipated and that she had been unable to gain weight. Her father died twenty years before of pneumonia. Her mother, aged 63, whom I also examined, was well, but had mild hypertension, with a blood pressure of 170 systolic and 90 diastolic. The mother had a slight, but noticeable enlargement of the left thyroid lobe. The patient's tonsils were removed at the age of 6. Her history was negative otherwise. Her menstrual history was normal and her previous health excellent.

General examination revealed a weight of 110 pounds (50 Kg.), a pulse rate of 120, a blood pressure of 180 systolic and 110 diastolic, slight enlargement of the right thyroid lobe and normal eyegrounds. The central nervous system was normal. Urinalysis disclosed a trace of albumin.

My clinical impression on the first visit was that I was dealing with idiopathic hypertension, possibly nephrosis (the diabetes albuminuricus of Epstein), so I gave the patient a diet high in protein and instructed her to report to me in two weeks.

On the occasion of the second visit, on July 29, I elicited the history of hyperhidrosis and the inability to gain weight. The persistent high pulse rate of 120 and the persistent hypertension of 176 systolic and 108 diastolic called my attention to the slight enlargement of the right thyroid lobe. My diagnosis at this time



Fig. 1.—Thyroid tissue. The left and right lobes are cut across and opened like a book. The capsule was smooth and nonadherent, and the consistency was firm. The cut surfaces exhibit a gland diffused throughout with small, yellowish-white, opaque lymph follicles, of various sizes. The gland substance is pink between the follicles and poor in colloid; reduced from a magnification of  $\times 2$ .

was hyperthyroidism with hypertension. Because of the otherwise excellent clinical condition of my patient, her weight being about the same (109.5 pounds [49.8 Kg.]), I permitted her to take a previously planned trip to California. I continued the diet high in protein, advised as much rest as possible and prescribed no thyroid medication. It was understood that on her return tests of thyroid and renal function would be made.

On September 21, the patient reported back to me. A postcard in the interim stated that she felt well. On September 21 she was still feeling well, was not as

constipated as previously and had gained weight. Her weight was 115 pounds (52.3 Kg.), the pulse rate 100, with occasional extrasystoles, and the blood pressure 196 systolic and 112 diastolic.

On September 22, the basal metabolic rate was plus 43, urea nitrogen 15.7 mg. per hundred cubic centimeters of blood, creatinine 1.7 mg. and blood chlorides 515 mg. The urinalysis disclosed a trace of albumin, a few leukocytes, a moderate number of red blood cells and no sugar. I recommended subtotal thyroidectomy, and the patient was hospitalized the following day, at the Barnert Memorial Hospital, Paterson, N. J.

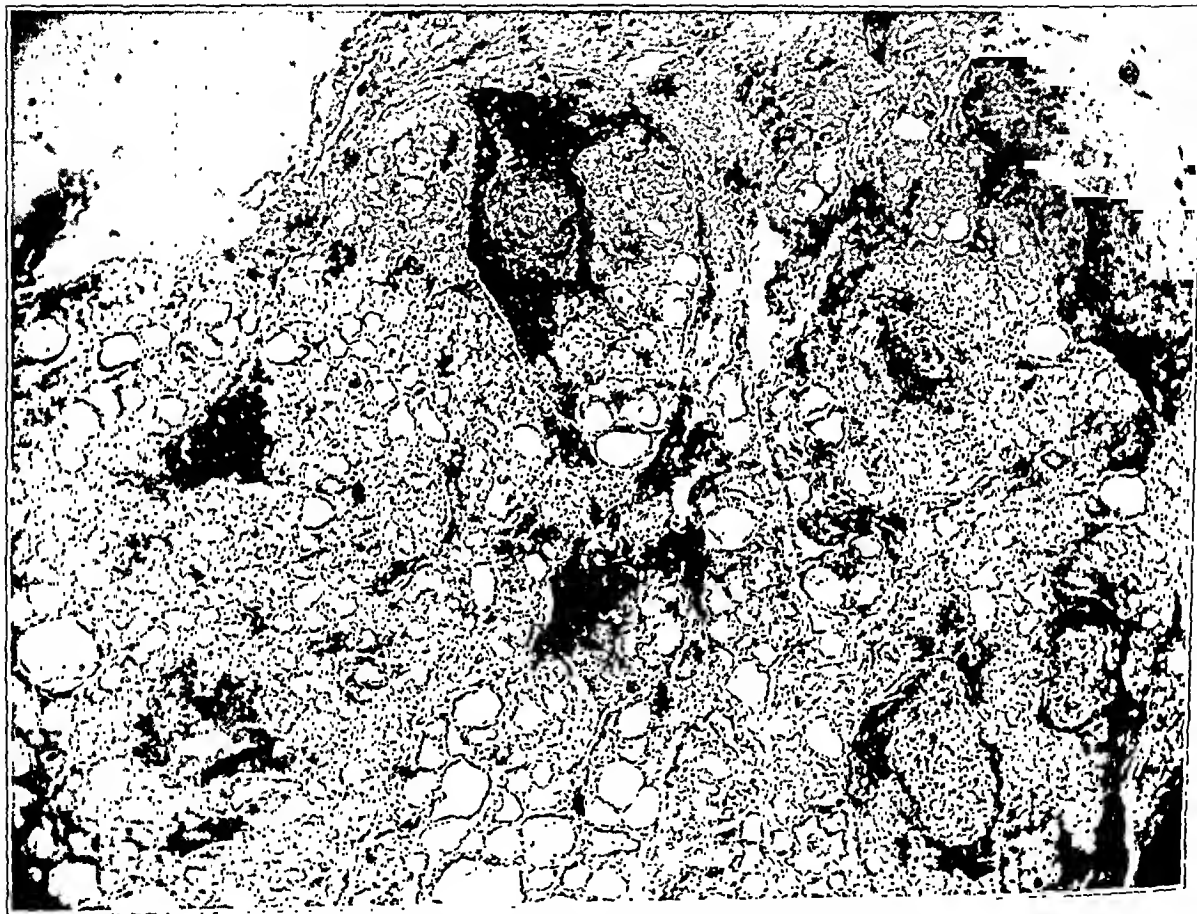


Fig. 2.—A low magnification of the removed thyroid tissue. The outstanding characteristic is the widespread lymphoid infiltration, with several lymph follicles. This could be seen in every microscopic field, the germinal centers being large and clear, with streams of lymphoid cells emanating from them and by their sinus paths delimiting entire gland units. One such glandular unit is clearly seen in the top center. Irregular aggregates of lymphoid tissue may be seen throughout the gland. Fibrosis is not a conspicuous feature; reduced from a magnification of  $\times 27$ .

During the subsequent four days of rest and preoperative preparation further laboratory examination revealed: red blood cells, 4,750,000; hemoglobin, 98 per cent; white blood cells, 7,050; lymphocytes, 31 per cent; transitionals, 4 per cent; eosinophils, 2 per cent, and neutrophils, 63 per cent; coagulation time, five minutes;

bleeding time, two minutes; Wassermann reaction (Mcinicke's modification), negative, and blood cholesterol, 195 mg. per hundred cubic centimeters of blood, the determination for cholesterol being made at the New Jersey College of Pharmacy, Newark, N. J.

On September 28, I performed a subtotal thyroidectomy. The operation was begun at 8:30 a. m. and closed at 10:10 a. m. Local anesthesia and ethylene and oxygen were used, the latter being administered by Dr. H. M. Stein. The gland was not adherent to the surrounding structures. A prominent pyramidal lobe was noted. The lack of hemorrhage was commented on, a feature I subsequently found

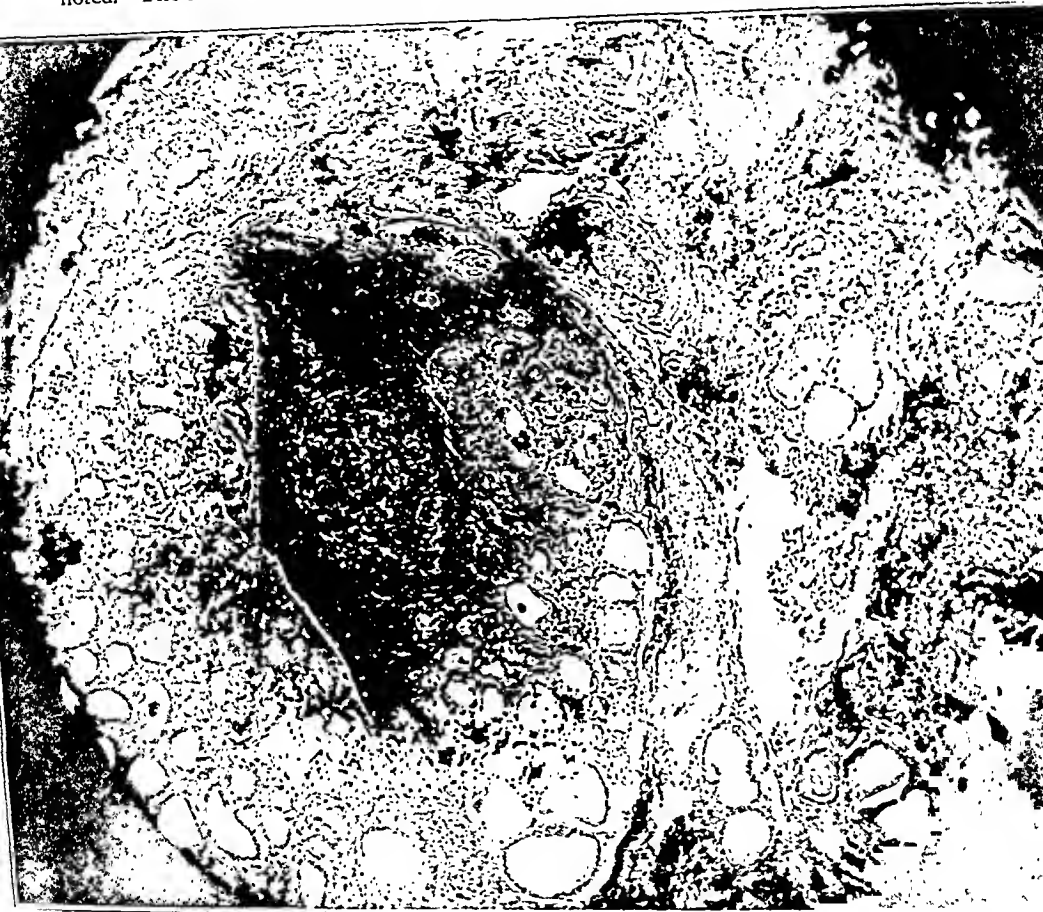


Fig. 3.—Higher magnification of the gland unit seen at the top center of figure 2. A large lymph follicle with a germinal center is seen at the hilus of the gland unit, with lymphoid tissue streaming away through the lymph channels which delimit the gland. Within the gland unit the lymphoid tissue has claimed most of the fields, thus impairing the thyrogenous function of the follicles within the gland unit, so that the colloid is much diminished or entirely absent; reduced from a magnification of  $\times 54$ .

to have been observed by other authors when operating on thyroid glands with a similar pathologic process. About one half to three fourths of the right lobe, the lower portion of the isthmus and pyramidal lobe and about one half the left lobe were resected (fig. 1).



The pathologic observations as reported by the pathologist, Dr. H. Wassing, were as follows: There were two specimens, one from the right and one from the left lobe of the thyroid gland, each the size of a prune. The surface was smooth, showing the thyroid capsule except for the part along which the resection was per-

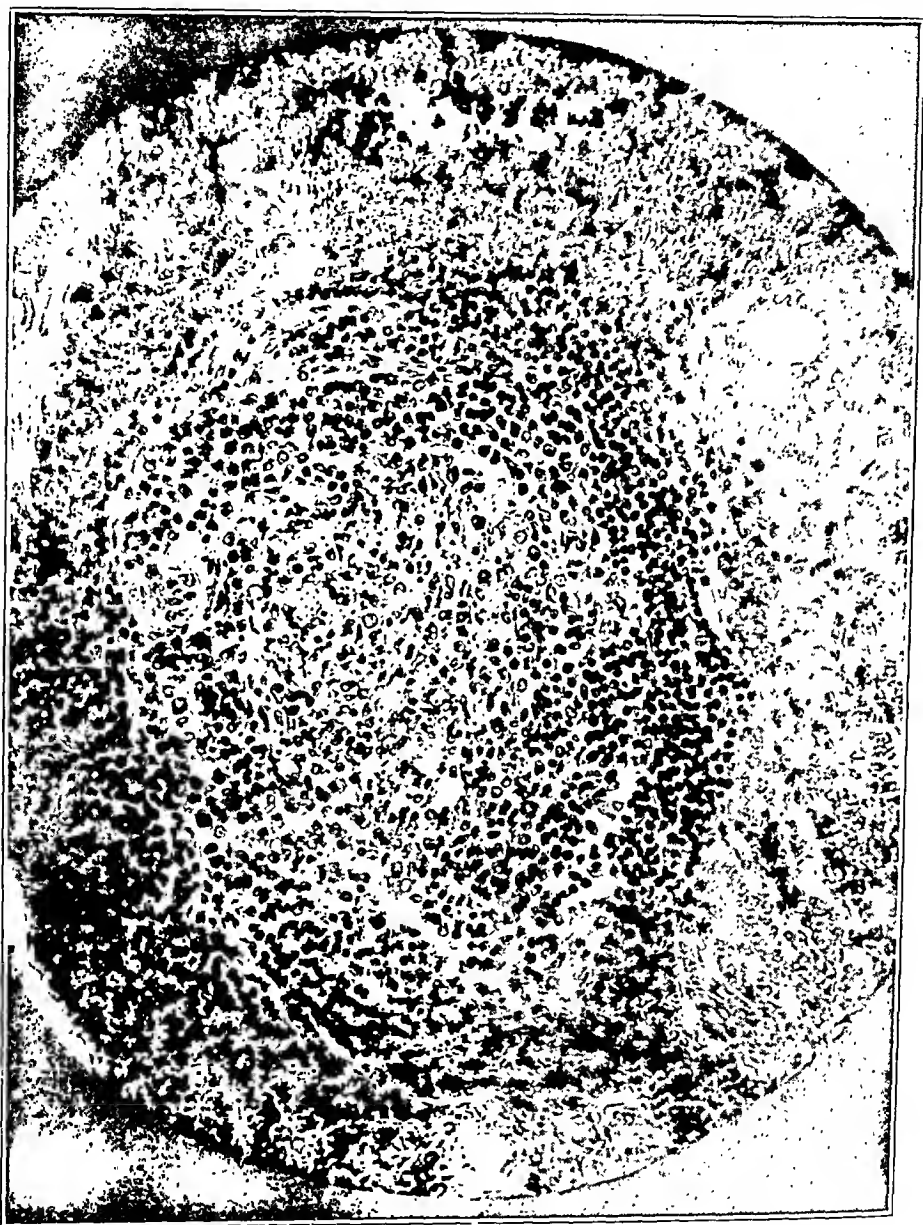


Fig. 4.—Oil immersion of the germinal center in the lymph follicle at the hilus of the gland unit shown in figure 3. Cells undergoing active mitosis may be picked out here and there in the center of the field; reduced from a magnification of  $\times 243$ .

formed. There and on other cross-sections a diffuse, finely granular surface was seen, apparently poor in colloid; there were many whitish opaque small foci, like lymph follicles. On microscopic examination one saw hypertrophic (toxic) struma, with

many areas in which colloid was absent and in which there were relatively larger, cuboidal or polyhedral follicular cells; a few areas showed an attempt at formation of folds of the epithelium. The outstanding feature was the enormous lymphoid infiltration, with several lymph follicles in every field, with large germinal centers; there also were a few areas in which the lymphoid tissue seemed to be diffusely infiltrating, but there was no evidence of true lymphogranuloma.

Except for an immediate crisis of moderate severity the postoperative course was uneventful. The patient left the hospital on October 6. On that day the

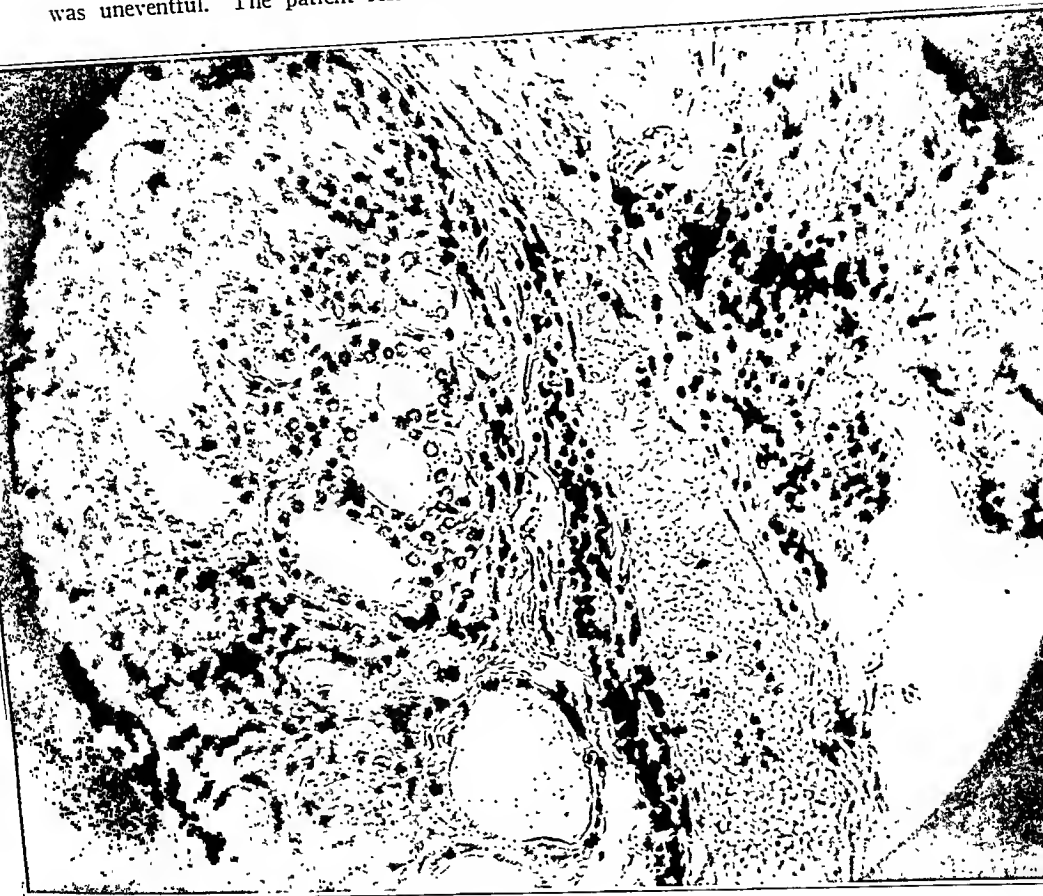


Fig. 5.—Oil immersion of the lymph sinus and blood capillary delimiting the right edge of the gland unit shown in figure 3. Several aggregates of lymphoid tissue may be seen in the blood capillary. Toward the lower edge of the photomicrograph is a lymph cell in the act of squeezing through the capillary wall, thus effecting its escape from the lymph sinus; reduced from a magnification of  $\times 243$ .

basal metabolic rate was plus 26, the pulse rate 100, the blood pressure 164 systolic and 100 diastolic and the weight 115 pounds. There was a marked decrease in hidrosis.

On November 25, the basal metabolic rate was plus 35, the pulse rate 120, the blood pressure 200 systolic and 120 diastolic and the weight 119.5 pounds (54.3 Kg.). The nocturnal hyperhidrosis complained of preoperatively had disappeared. The administration of compound solution of iodine appeared to make the patient

perspire. I discontinued the use of iodine, and the patient became free from this annoying symptom. I cannot account for the persistent elevation of the basal metabolic rate and pulse rate and the hypertension. The patient stated that she felt better than before, and she gained weight. The last-mentioned weight is more than she ever weighed.

#### PROGNOSIS

Joll<sup>5</sup> stated that myxedema is the ultimate clinical feature, though it failed to develop in one case he observed for years. He stated that myxedema quickly follows resection of the gland. Williamson and his associates<sup>2</sup> stated that progressive symptoms rarely appear before the age of 45, while myxedema occurs on an average of a decade later. They performed a necropsy on a man, aged 65, whose thyroid gland exhibited early struma lymphomatosa and whose history disclosed no coexisting myxedema.

#### TREATMENT

It is too soon to judge, on the basis of this one case, the efficacy of thyroidectomy during the early stage of struma lymphomatosa associated with hyperthyroidism. Thus far the patient is definitely improved. In the light of McCarrison's experimental work on rats, previously mentioned, prophylaxis in the form of a diet rich in vitamins seems advisable. Iodine appears not to be helpful. Furthermore, it is obvious that in the present state of knowledge a preoperative diagnosis of struma lymphomatosa associated with hyperthyroidism cannot be made. However, in the later stages of the disease Joll and his associates believed that a diagnosis can be made, especially when in association with hypothyroidism. When so made, thyroidectomy is contraindicated unless the pressure on the trachea interferes greatly with the patient's activities. Joll suggested the administration of dried thyroid gland as a post-operative therapeutic measure, with regular check-ups on the basal metabolic rate as a guide.

#### COMMENT

It is well known that in exophthalmic goiter the thyroid gland is frequently invaded by lymphoid tissue, with definite lymphoid nodules often found scattered through the gland. Usually associated with such a change there is local and distant lymphadenitis, even the lymph nodules in the intestine being involved (MacCallum<sup>8</sup>). There is also associated distinct lymphocytosis. But the outstanding pathologic change in exophthalmic goiter is the reduplication of epithelium, the lymphoid invasion of the gland being only a secondary microscopic observation and quantitatively usually negligible. The pathologic picture in struma lymphomatosa associated with hyperthyroidism as found in my

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8. MacCallum, W. G.: *A Text-Book of Pathology*, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 881.

case presents a striking contrast. Both macroscopically and microscopically (figs. 1 to 5) the lymphoid invasion of the gland was the outstanding pathologic change. This was not associated with local or distant lymphadenitis; it was not associated with distinct lymphocytosis, and there was no reduplication of follicular epithelium.

#### SUMMARY

I believe this to be the first case of struma lymphomatosa associated with hyperthyroidism to be reported. As such it furnishes an important link in the pathogenesis of struma lymphomatosa when associated with no thyroid or hypothyroid symptoms. The clinical and pathologic features are described and treatment suggested.

#### CONCLUSIONS

1. Struma lymphomatosa (Hashimoto) is a distinct pathologic entity of rare incidence. 2. Thyroidectomy is indicated when the condition is associated with hyperthyroidism or when it is associated with symptoms referable to compression of the trachea. 3. Thyroidectomy is contraindicated when the condition is associated with no thyroid symptoms or hypothyroidism.

# CARTILAGINOUS EXOSTOSIS OF THE SCAPULA

## REPORT OF TWO CASES

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AND

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Osseous growths capped by a layer of hyaline cartilage frequently occur about the epiphyses of long bones but also occasionally in flat bones. They are usually multiple and are believed to originate from misplaced islets of epiphyseal cartilage and thus appear during skeletal development and cease growing when the latter is completed. A solitary cartilaginous exostosis of the scapula with no growths elsewhere is rare. A review of the available literature yielded records of less than twenty instances. In this article two cases recently observed in the New Haven Hospital are reported.

## REPORT OF CASES

CASE 1.—A Negro boy aged 7 years was admitted to the New Haven Hospital on March 13, 1928, with the complaint of prominence of the left scapular region. According to the mother this was first noted when the child was 4 years old. Since then the deformity has increased slightly and caused some pain occasionally but no apparent interference with the motions of the shoulder. A history of rickets, tuberculosis or syphilis was not obtained. The family history was not contributory; six brothers and three sisters were living and well. On admission the child appeared to be healthy, well developed and well nourished, presenting nothing unusual except the prominence of the left scapular region. The inferior angle appeared elevated, projecting posteriorly about 2 cm. above the level of the right scapula. Attached to the costal surface of the inferior angle, a firm, irregular mass, the size of a golf ball, was felt. This mass was not tender or painful and did not interfere except with the extreme motions of the shoulder. Roentgenographic examination revealed a deformity of the lower third of the left scapula suggesting a bony prominence. A diagnosis of osteochondroma of the left scapula was made, and on March 16, the infrascapular portion of the shoulder blade together with the tumor was removed by Dr. Winthrop M. Phelps.<sup>1</sup>

The resected portion of the scapula was triangular and measured 5.5 by 5.5 by 5 cm. Attached to its anterior surface was a somewhat nodular bony prominence shaped like a mushroom, the head of which was covered with cartilage and measured from 3.5 to 4 cm.; the stem was from 2.5 to 3 cm. in diameter. Cartilaginous and tendinous tabs were attached to the stem. A sagittal sawcut through the midportion of the specimen showed that it consisted of cancellous bone rimmed by a narrow zone of compact bone. In an area 1 cm. in diameter the

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From the Department of Pathology and the Department of Surgery, Yale University School of Medicine.

1. Phelps, Winthrop M.: A Method of Resection of the Infra-Spinous Portion of the Scapula Without Impairment of Shoulder Muscle Function, *Yale J. Biol. & Med.* 2:39, 1929.

central portion contained soft marrow. A microscopic preparation of the entire sagittal section (fig. 1) showed well formed cancellous bone rimmed on the sides by a narrow zone of compact bone and capped by a layer of hyaline cartilage. The latter merged in a perfectly regular manner with the underlying cancellous bone. No bony lamellae were present in the central portion of the elevation, and the space was filled with bone marrow. At the base the cancellous bone merged with the scapula.

The patient made an uneventful recovery and was discharged on April 2, 1928. When he was seen one year later there was no limitation of motion or weakness

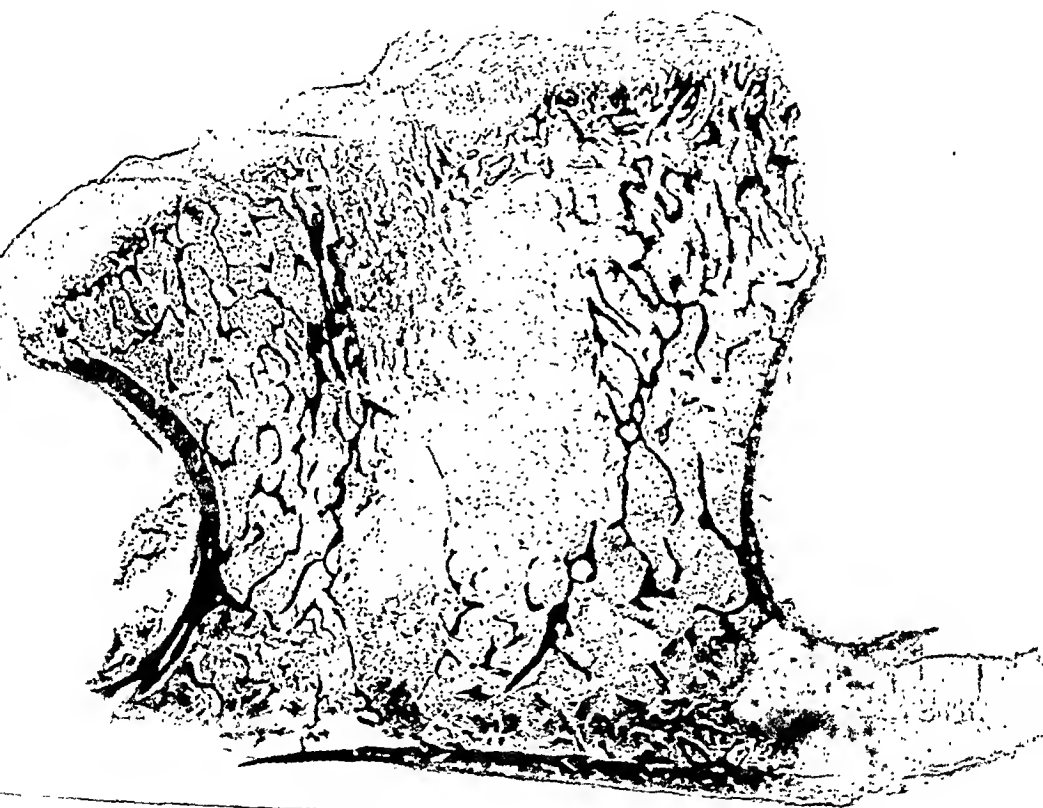


Fig. 1.—Microscopic preparation of a sagittal section through the midportion of a cartilaginous exostosis of the scapula in a 7 year old Negro boy;  $\times 3$ . The growth consists of cancellous bone rimmed on the sides by a narrow zone of compact bone and capped by a layer of hyaline cartilage.

of action in any of the muscles of the shoulder. Three years later there had been no recurrence of the growth.

CASE 2.—A girl aged 16 years was admitted to the New Haven Hospital on Sept. 11, 1933, complaining of a painful tender growth on the back of her right shoulder, which had been present for over three years. When first noted the deformity was thought to be due to bad posture. The growth increased slowly and was accompanied by a dull aching pain and tenderness, but caused no limitation of the movements of the shoulder. The past and family histories were noncontributory. Two brothers and two sisters were living and well.

On admission the patient appeared well developed and well nourished, and except for the prominence of the right scapular region, presented no abnormality. At about the medial angle of the scapula there was a bony prominence the size of a "small orange" projecting toward the ribs. There was a grating on motion of the scapula, but no limitation of movements. Roentgenographic examination revealed a bony prominence with a cancellous structure attached to the subscapular surface of the scapula near the medial angle. A diagnosis of exostosis of the scapula was made, and on September 12 the medial angle of the scapula together with the attached growth was resected by Dr. Samuel C. Harvey.

The removed portion of the scapula measured 5.5 by 3 by 1 cm. Attached to its concave surface was a mushroom-shaped bony spur capped by cartilage. The head measured 2.5 by 1.5 cm. in diameter; the stem was 1.7 cm. thick. The spur projected 2 cm. above the surface of the scapula. A sagittal sawcut showed the



Fig. 2.—Microscopic preparation of a sagittal section through the midportion of a cartilaginous exostosis of the scapula in a 16 year old girl;  $\times 3$ . The growth consists of cancellous bone with well formed lamellae and marrow spaces bordered by a thin layer of compact bone on the sides and covered on the free surface by a layer of hyaline cartilage.

spur to be composed of cancellous bone covered on the sides by compact bone, merging with the scapula at its base and covered by cartilage on the opposite surface. A microscopic preparation of the spur (fig. 2) showed cancellous bone with well formed lamellae and marrow spaces bordered by a thin layer of compact bone on either side. The spur continued into the scapula at the base. The opposite surface was covered by a layer of hyaline cartilage. Along the chondro-osseous junction which was fairly straight there was a suggestion of formation of new bone.

The patient was discharged on the seventh day (September 19) following the operation. When seen four months later she had no complaints and no impairment in function of her shoulder.

REPORT OF CASES FROM THE LITERATURE

BEAUMONT.—The first case of cartilaginous exostosis of the scapula was reported by Beaumont<sup>2</sup> in 1838. A boy aged 13 years was seen "on account of a very considerable projection of the inferior angle of the right scapula, attended with pain after exertion, loss of power, and diminished freedom of motion in the right upper extremity." Recently the tumor had increased in size and "the patient began to be incapable of following his occupation, in which he was frequently obliged to lift and carry parcels of considerable weight." The inferior angle of the scapula was "thrown out from the ribs nearly two inches above its level, which was caused by a tumor, the size of a large walnut" attached to the costal surface of the inferior angle of the scapula. On account of the hardness of the projecting portion and of its unyielding attachment to the scapula it was thought to be an exostosis. On July 5, 1838, the tumor was removed, together with a portion of the scapula to which it was attached. The growth consisted of cancellous bone with areas of firmer osseous tissue; its entire free surface was covered by a thick layer of cartilage—"as hard and compact as articular cartilage." Between nine and ten weeks after the operation the patient was "free from pain, and his right arm had become as strong as the other and possessed the same extent and freedom of motion"—and "for two weeks past he resumed his former occupation."

PEPPER.—The second case of cartilaginous exostosis of the scapula was presented before the Pathological Society of Philadelphia on Oct. 24, 1867, by George Pepper.<sup>3</sup> A specimen removed at necropsy of a 16 year old colored boy who died of tuberculosis was shown. Prominence of the right scapula had been noted during life though it had caused no symptoms. "The growth sprang from the under surface of the bone, close to the posterior border, and about midway between the upper and lower angles." It had a mushroom-like appearance with a broad sessile attachment and thick overhanging edges. It measured 1½ by 1 inches (3.81 by 2.54 cm.) and was elevated about 1 inch above the surface of the bone, which seemed normal. On section the pedicle was seen to have an osseous structure; the body was partly osseous and partly calcareous, overlaid by a thin layer of cartilage. The gross observation was verified by microscopic examination.

BIRKETT.—In 1869 Birkett<sup>4</sup> mentioned in his presentation of cartilaginous and bony growth that he had seen three patients with exostoses of the scapula: "a boy twelve years of age, and two girls, one sixteen years old, the other twelve. In the first the growth had been observed four months, in the second three years, in the third one year. The tumors were small and do not require any particular description."

RICHET.—In 1885 Richet<sup>5</sup> removed an exostosis of the scapula from a boy 12 years old. The growth had been noted as a small swelling five or six years previously, and since that time it had not increased in size or caused any discomfort.

2. Beaumont, William: Exostosis of Scapula, *London M. Gaz.* **23**:162, 1838.

3. Pepper, George: Osteo-Enchondroma of the Venter of the Right Scapula, *Am. J. M. Sc.* **55**:400, 1868.

4. Birkett, John: Cartilaginous and Bony Growths: Exostoses on the Bones of the Upper Extremity, *Guy's Hosp. Rep.* **14**:499, 1869.

5. Richet: Exostose de l'angle inférieur de l'omoplate, *France médicale* **32**:400, 1885.



HEURTAUX.—In November 1885, at a meeting of the Société Anatomique de Nantes, Heurtaux<sup>6</sup> described a scapula with a cartilaginous exostosis removed from a man, 24 years old. The growth was attached to the spine of the scapula by a slender pedicle, had the form of a "coracoid process," and consisted of cancellous bone covered by a broad layer of hyaline cartilage.

VON KÖLLIKER.—In 1891 von Kölliker<sup>7</sup> reported two cases of "congenital upward displacement of the shoulder blade," ascribed to exostosis of the scapula. The first patient, a boy, aged 10 years, had an exostosis on the medial angle of the right scapula which caused an upward and lateral displacement of the latter and resulted in a "scoliosis cervico-dorsalis dextroconvexa." The second patient, a boy aged 4 years, had an exostosis somewhat lateral from the medial angle of the left scapula. The hook or finger-like projection extended about 2 cm. over the clavicle. This drew the scapula upward, and a dorsal scoliosis, convex to the left, developed. In neither case was there any limitation of movements. Operative treatment was refused by the parents of both children.

KÖNIG.—In 1893, in discussing Schlang's paper on upward displacement of the scapula, presented at the twenty-second congress of the Deutsche Gesellschaft für Chirurgie, König<sup>8</sup> reported the case of a 7 year old girl. One scapula was markedly displaced upward, and a loud cracking was heard on certain movements of the shoulder. The patient had marked scoliosis. An operation disclosed an exostosis attached to the scapula in such a manner that it touched the second rib and thus interfered with the movements of the extremity. The exostosis was removed in the belief that it was the cause of the upward displacement.

ROBINSON.—In 1899, Robinson<sup>9</sup> reported an exostosis of the scapula in a girl aged 9 years. She had had the swelling nearly all her life. There was no complaint of pain or of any inconvenience. The right scapula appeared "winged," its inferior angle being raised off the chest wall and displaced upward and outward. The vertical distance from the spine to the inferior angle was 1 inch (2.54 cm.) less than on the left side. Just above the inferior angle of the scapula a hard nodular tumor with a base 2 inches (5.08 cm.) across was attached to the vertebral border. It caused no limitation of movements. The tumor removed on June 28, 1898, "was a typical cancellous exostosis, with a very marked cartilaginous cap growing from the epiphyseal line between the scapula and its vertebral border, and was about the size of a tangerine orange." When the patient was seen three months later all muscular movements were "perfect."

IRIBARNE.—In 1900 Iribarne<sup>10</sup> reported the case of an 8 year old girl who was seen on June 18, 1898, on account of a growth in the left scapular region; this was first noted when she was 8 months old. Since then the growth had increased in size causing deformity and some limitation of certain movements. The head was

6. Heurtaux, M.: Exostose de croissance de l'épine de l'omoplate, *J. de méd. de l'ouest* 20:384, 1886.

7. von Kölliker, T.: Bemerkungen zum Aufsätze von Dr. Sprengel "Die angeborene Verschiebung des Schulterblattes nach oben," in diesem Archiv, Band 42, Heft 3, *Arch. f. klin. Chir.* 42:925, 1891.

8. König: *Verhandl. d. deutsch. Gesellsch. f. Chir.* 22:68, 1893.

9. Robinson, H. Betham: Exostosis of the Vertebral Border of the Scapula: Removal, *Brit. M. J.* 2:963, 1899.

10. Iribarne, Joseph: Contribution à l'étude des exostoses ostéogéniques, Thèse de Paris, 1900.

tilted to the right; there was a slight scoliosis with the convexity to the left. The left shoulder was elevated, and the inferior angle of the left scapula was four fingerbreadths above that of the right. A triangular tumor was located on the posterior surface of the left scapula along the vertebral border at the middle of the lower third. It measured from 3 to 4 cm. in height. Movements were free except that elevation of the arm was arrested at less than 45 degrees. The tumor was thought to be an exostosis and was resected by Broca. Nine months following the operation the left scapula was still elevated.

GANTCHEFF.—In 1901 Gantcheff<sup>11</sup> reported an exostosis of the scapula in a 7 year old boy. A prominence in the region of the left scapula was first noted three months previously and was thought to be due to scoliosis. The deformity did not seem to increase. On examination there was no scoliosis. The vertebral border of the scapula was elevated owing to a bony tumor about 5 cm. in diameter at its base attached to the costal surface of the scapula near the vertebral border. The movements of the shoulder were not impaired. There was a suggestion of a slight osseous prominence in the region of the spine of the same scapula, but none elsewhere. The growth removed on June 7, 1900, measured 3 cm. in height, had the shape of a "champagne bottle," and consisted of cancellous bone covered by cartilage.

FERBOS.—In the case reported by Ferbos,<sup>12</sup> in 1906, the patient was under Guyot's care. A girl aged 15 years complained of a deformity of the right scapular region, which had been present for several years. No history of trauma was obtained. The father and mother, two brothers and two sisters were living and well. Attached to the scapula on the vertebral border a firm elevation about 4 by 5 cm. was noted. This scapula measured 1 cm. less in the horizontal and vertical directions than the normal left scapula. A diagnosis of exostosis of the scapula was made, and the tumor was removed two months following the first examination. The specimen consisted of a bony spur, with the free surface covered by a bursa. The peripheral portions were dense, the central portion spongy, with no medullary cavity. The patient made a good recovery, and when she was seen ten months following the operation there was no pain or recurrence of the growth.

MCWILLIAMS.—In 1914, McWilliams<sup>13</sup> reported the following case: A girl aged 18 years complained of dull aching pains in the left shoulder and of a grating or creaking sound on drawing the scapula backward and forward; the condition had been present for one year. The patient stated that twelve years previously, following a fall, the left scapula began to become prominent. For this condition she wore a brace for a year without any benefit. A swelling was noted just inside the scapula. On examination the left scapula was prominent with a fulness at the lower part where an indefinite swelling about the size of a lemon was felt which extended forward beneath the scapula. A roentgenogram showed an "exostosis on the inner side of the lower part of the left scapula." At operation the growth seemed to be partially surrounded by a bursa. The specimen removed was about 4 cm. long, with a broad oval end covered by cartilage and a narrow pedicle by which it was attached to the scapula. Microscopic examination showed the growth

11. Gantcheff, Georges: *Etude sur les exostoses de l'omoplate*, Thèse de Lyon, 1900-1901, no. 163.

12. Ferbos, H.: *Des exostoses de l'omoplate*, Thèse de Bordeaux, 1906.

13. McWilliams, Clarence A.: *Subscapular Exostosis with Adventitious Bursa*, J. A. M. A. 63:1473 (Oct. 24) 1914.

to be composed partly of bone and partly of cartilage. Two months following the operation the appearance of the shoulder and the position of the scapula appeared normal, and there was no pain on motion.

PEAK.—In 1914, Peak<sup>14</sup> reported the case of a girl aged 7 years whose mother noted that for the previous three years the child's right shoulder blade seemed to increase in size. The tumor was attached to the costal surface about midway between the lower angle and the spine. Microscopic examination of the removed growth showed it to be an "osteochondroma."

BROWN.—In 1916, Brown<sup>15</sup> reported a case of cartilaginous exostosis of the scapula in a 16 year old girl. She complained of prominence of the right shoulder, present for two or three years. The condition became more noticeable and painful a few weeks preceding the examination. No history of trauma was obtained. The right shoulder was prominent; crepitation could be elicited, and it was noted that at times the scapula in sliding over the ribs would "catch and jump from one rib to another." This was associated with pain. During the subsequent one and a half years the patient was treated with exercises and braces. Since these measures proved ineffective the upper part of the right scapular region was exposed, and the medial angle of the scapula was resected together with a "hook-like process of bone" attached to its anterior surface. The removed portion of the scapula showed a backward bend of the medial angle and a bony prominence, "a little over 3 cm. in length," on its anterior surface attached at right angles by a broad triangular base. The middle portion or shaft was also triangular but smaller than the base or the free rounded end which was covered by a "white glistening cartilage-like material." The specimen was not submitted to microscopic examination. The patient made an uneventful recovery, and when seen five months following the operation she was "perfectly well as far as the shoulder was concerned."

GÉNÉVRIER.—In 1923, G  n  vri  r<sup>16</sup> presented before the Soci  t   de P  diatrie de Paris a case of exostosis of the scapula. The patient, a boy, aged 12 years, had a growth the size of a "mandarine" which was attached to the vertebral border of the right scapula. The growth was known to exist by the parents and the boy, but no attention was given to it. It caused no symptoms. It was incidentally discovered when roentgenograms of the chest were taken for a condition of the bronchi.

#### COMMENT

A cartilaginous exostosis is an osteochondroma—a benign neoplasm—in which the tissue components reproduce their normal structures and retain their orderly relations. Growth occurs in them at the chondro-osseous junction by endochondral formation of bone. The growth apparently occurs with equal frequency on either scapula of males or females. The location is on the vertebral border near the inferior angle or about other junctions of centers of ossification. This and the

14. Peak, I. Hunter: Osteo-Enchondroma of the Scapula, Kentucky M. J. **12**:800, 1914.

15. Brown, Lloyd T.: An Unusual Exostosis of the Scapula, Boston M. & S. J. **174**:652, 1916.

16. G  n  vri  r, M.: Exostose de l'omoplate, Bull. Soc. de p  diat. de Paris **21**:47, 1923.

fact that the tumors behave like the exostoses of long bones support the view that they arise from accessory centers of ossification.

#### SUMMARY

Two cases of cartilaginous exostosis of the scapula with no growths elsewhere are presented, and similar cases gathered from the literature are reviewed.

# INFLUENCE OF A DIET RICH IN CASEIN ON THE STRENGTH OF BONE AND THE HEALING OF FRACTURES

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It has become increasingly evident from our studies on the rat that the beam strength of the fibula varies in general with the body weight. When, for example, we plotted the strength of the fibulas of normal rats selected at random as a function of their body weight, the strength of the bones increased as the weight increased.<sup>1</sup> Again, when we started rats of approximately the same age on a diet on which it happened that they lost weight because they progressively ate less, their fibulas lost strength likewise.<sup>2</sup> It seems, therefore, that there is a definite strength of bone per unit of body weight, and that the strength of the weight-bearing bones varies directly with function (Wolff's law).

In spite of this general relationship between the strength of bone and the body weight, however, the ratio of the one to the other can be altered experimentally. The food ingested naturally influences the strength of bone by changing the body weight and changing the function of weight bearing, but undoubtedly it also influences the strength of bone directly. Burnett,<sup>3</sup> for example, fed hogs on a diet rich in tankage or bone meal and obtained an increase in the size and strength of bones out of proportion to the gain in body weight. The bones of the control animals fed alfalfa did not exhibit these changes.

The skeleton is the storehouse for the ingested mineral salts, and not a static mass of these salts in an inorganic matrix. Its calcium

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The expenses of this investigation were defrayed by Davis and Geck, Inc.

1. Lindsay, M. K., and Howes, E. L.: *J. Bone & Joint Surg.* **13**:491 (July) 1931.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: *The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet*, *Arch. Surg.* **24**:458 (March) 1932.

3. Burnett, E. A.: *Twenty-Fourth Annual Report of Agricultural Experiment Station, University of Nebraska, 1911*, p. 178.

and phosphorus ions are in chemical equilibrium with similar ions of the blood. The direction of the flow of calcium salts in this blood-bone system depends on the supply of calcium and phosphorus and the solubility of these salts in the plasma.<sup>4</sup> Calcium salts can be withdrawn from bone when acids or parathyroid extract-Collip are given by mouth, and Bauer, Aub and Albright<sup>5</sup> have even demonstrated that the bony trabeculae are the readily available sources of calcium and phosphorus. Conversely, calcium can be deposited in bone by a diet rich in mineral salts or viosterol. Moreover, these fluctuations in the mineral salts of bone cause variations in their strength. For example, when the fibula is depleted of mineral salts either by immersion in an acid or by maintaining the animal on a diet low in salt, strength is lost.

The question naturally arises, then, whether the strength of bone and the healing of a fracture can be affected by changing of substances in the diet which affect the metabolism of the mineral salts. The calcium salts in the blood plasma occur in a supersaturated state, and this supersaturation has been attributed by Pryde to the fixation of both calcium and phosphorus ions in nondiffusible form by the proteins of the plasma.<sup>6</sup> These three constituents even have a mathematical relationship to one another. Peters and Eiserson found that the calcium in the blood serum varies directly with the concentration of protein and inversely with the concentration of inorganic phosphorus according to the formula, calcium =  $-0.255 \text{ phosphorus} + 0.566 \text{ protein} + 7$ . With such a balanced relationship, if it were possible to increase the amount of protein in the blood stream, there should be either an increase in the amount of calcium or a decrease in the amount of phosphorus, and a change in the ratio of bone strength to body weight. Actually, however, an excess of ingested protein is excreted as urea, and the blood remains chemically constant. It is the function of the blood stream to maintain constancy, and analyses of it do not indicate that more amino-acids have passed through it after the ingestion of a diet rich in protein than when this excess is not ingested. Likewise, the chemical constancy of the blood gives no idea as to whether the mineral salts are being carried from the gastro-intestinal tract to the skeleton or from the skeleton to the excretory channels. Variations in the strength of the bones should indicate, however, whether calcium salts have been deposited in the bones or removed from them, and we therefore felt justified in trying to change the strength of bone by a diet rich in protein.

4. Peters, J. E., and Eiserson, L. J.: *J. Biol. Chem.* **84**:155 (Oct.) 1929.

5. Bauer, W.; Aub, J. C., and Albright, F.: *J. Exper. Med.* **49**:145 (Jan.) 1929.

6. Pryde, John: *Recent Advances in Biochemistry*, Philadelphia, P. Blakiston's Son & Co., 1928.

## EXPERIMENTATION

The diet rich in protein consisted of 80 per cent of casein with sufficient vitamins and salts to give it adequacy (table 1). Its caloric content is somewhat lower than the standard diet fed to the control animals.

Rats weighing from 190 to 300 Gm. and approximately 6 months of age were used. The animals had grown normally since birth. They were kept in separate cages and put on the diets one week before the experiment was started. They were allowed to eat all they wished, and their weights were recorded throughout the experiments. The animals were divided into two groups on each diet. One group was placed on the diets in order to determine their effects on the strength

TABLE 1.—*Standard Diet*

Percentage Composition		Calories per Kilogram of Food	Apportionment of Total Calories	
	Per Cent			Per Cent
Standard Balanced Diet				
Casein.....	18	738	Protein.....	13.8
Starch.....	51	2,091	Carbohydrate...	39.2
Hydrogenated oil.....	22	2,046	Fat.....	47.0
Cod liver oil.....	5	465		
Salts (Mendel and Osborne mixture*).....	4	5,340		
High Protein Diet				
Casein.....	80	3,280	Protein.....	68.7
Hydrogenated oil.....	12	1,488	Fat.....	31.8
Cod liver oil.....	4			
Salts.....	4	4,768		
On both diets: Lettuce twice a week, 70 mg. of yeast daily				

On both diets: Lettuce twice a week, 70 mg. of yeast daily

\* The salt mixture consists of the following: calcium carbonate, 134.8 Gm.; magnesium carbonate, 24.2 Gm.; sodium carbonate, 34.2 Gm.; potassium carbonate, 141.3 Gm.; phosphoric acid, U.S.P., 103.2 Gm.; hydrochloric acid, 53.4 Gm.; sulphuric acid, 9.2 Gm.; citric acid plus water, 111.1 Gm.; crystallized iron citrate, 6.34 Gm.; potassium iodide, 0.020 Gm.; manganese sulphate, 0.079 Gm.; sodium fluoride, 0.248 Gm., and potassium aluminum sulphate, 0.0245 Gm.

of bone, and the right fibulas of the other group were fractured in order to study the effects of the diets on the healing process. The fractures were made by cutting the fibulas at their midpoints with scissors, and the fragments were left in the best possible alignment. The technic for this procedure has been described before.<sup>1</sup> At intervals of three days from the sixth to the fifty-fourth day five animals were killed from both groups on both diets. The soft parts were stripped from the fibulas, and the bones were fastened together in pairs with a tag bearing the body weight. After they were dried in a desiccator for one week, their strengths were determined on a testing apparatus devised for the purpose.<sup>1</sup> The apparatus consists of two supports across which the bone is suspended. The supports are mounted on the pan of a scale balance. With the bone in place, the breaking force is applied at a constant rate at two points equidistant from the support. The strengths of five tests were averaged for each interval and plotted as a function of time.

Roentgenograms were taken of typical calluses at each three day interval, and cross-sections of each were measured and examined with a binocular microscope.

# RESULTS AND COMPARISON OF CURVES

*Normal Fibula.*—The body weight and the strength of the fibulas are given in table 2.

The ratios of the body weight to the strength of the fibulas are plotted in figure 1. Those for the rats on the diet rich in casein fluctuate

TABLE 2.—*Strength of Normal Fibulas and Body Weight*

Experimental Days	Standard Diet			Diet Rich in Casein		
	Weight at Death	Left	Right	Weight at Death	Left	Right
6.....	261	643	608	224	291	293
9.....	294	509	484	209	480	435
12.....	226	415	420	239	532	475
15.....	204	306	305	235	530	573
18.....	196	289	279	260	566	498
21.....	232	403	339	213	501	511
24.....	232	560	555	232	491	418
27.....	212	490	458	211	413	383
30.....	221	366	356	244	604	536
33.....	205	268	294	216	520	505
36.....	201	321	266	246	569	744
39.....	225	393	363	258	465	403
42.....	211	415	420	245	840	771
45.....	208	434	416	215	379	354
Averages.....	223.4	415.1	399.3	223.4	533.0	496.6
Ratio.....		1.85	1.70		2.25	2.10

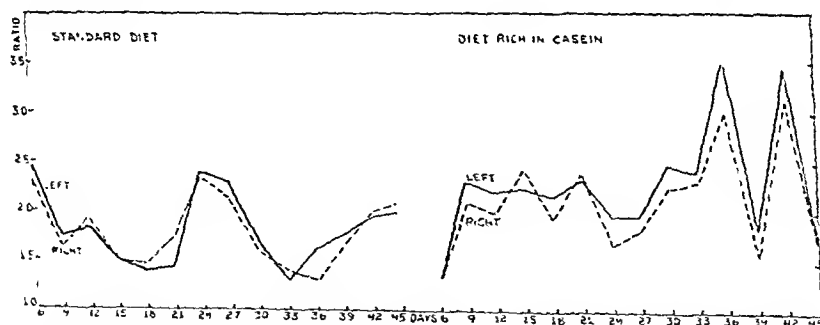


Fig. 1.—Ratio of the body weight to the strength of the fibulas of animals fed the standard diet and those fed a diet rich in casein.

like those for the rats on the standard diet, but they are in general greater. The strength of the fibula, therefore, has been increased in proportion to the body weight by the ingestion of the diet rich in casein.

*Fractured Fibula.*—The breaking strength of the healing fractures and of the opposite uninjured fibulas is given in table 3. The curves of the ratios of these to the body weights are given in figure 2.

In the previous publications we described the curve of the healing strength of the fractured fibula of the adult rat fed on the standard



diet. This curve had four distinct phases corresponding to the anatomic changes taking place during healing. In the first phase of fibrinous and early fibrous union, from the first to the sixth day, the callus had no strength. In the second, until the fifteenth or twentieth day, there was a rapid increase in its strength as the late fibrous union progressed and the "primary callus" was deposited. During the subsequent interval, or the third phase, the strength decreased as the callus organized.

TABLE 3.—*Strength of Fractured Fibulas and Opposite Uninjured Fibulas*

Postoperative Days	Standard Diet		Diet Rich in Casein	
	Left	Right	Left	Right
6.....	464	57	318	51
9.....	464	217	339	231
12.....	505	253	414	247
15.....	625	401	371	217
18.....	428	261	475	263
21.....	326	244	417	217
24.....	457	260	385	304
27.....	418	283	279	254
30.....	359	302	378	310
33.....	413	295	361	266
36.....	539	353	310	413
39.....	530	349	382	333
42.....	366	311		
45.....	463	441		

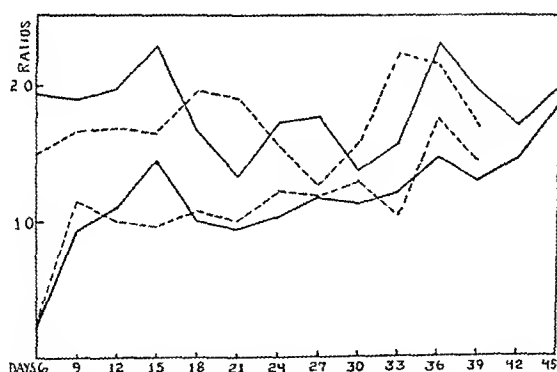


Fig. 2.—The ratio of the strength of the right and left fibulas to the body weight of animals fed the standard diet is represented by the solid line; that of animals fed a diet rich in casein, by the dotted line. The two upper curves are for the left uninjured fibulas; the lower two for the right fractured fibulas.

Finally, however, as organization was completed and the cortex reformed and realinement of the fragments took place, there was again an increase in strength. At the end-point the ultimate strength of the callus was greater than that of the rest of the bone, although until this point was reached the callus had broken, except in a few isolated instances, when

apparently some weakness in the rest of the bone had caused the break to occur elsewhere. The end-point occurred on the forty-fifth day.<sup>7</sup>

On this diet rich in casein, the curve of the ratios is quite different from that obtained for the standard diet. The end-point is reached on the thirty-ninth day, a shortening of six days, and the initial rise is more rapid, although its peak is not so high. Consequently, the subsequent loss is not so great. From the eighteenth day on, the curve steadily mounts in strength approximately at the same rate as the standard curve. It is of interest to note also that the curves for the diet high in protein exhibit a parallelism between the strength of the right and that of the

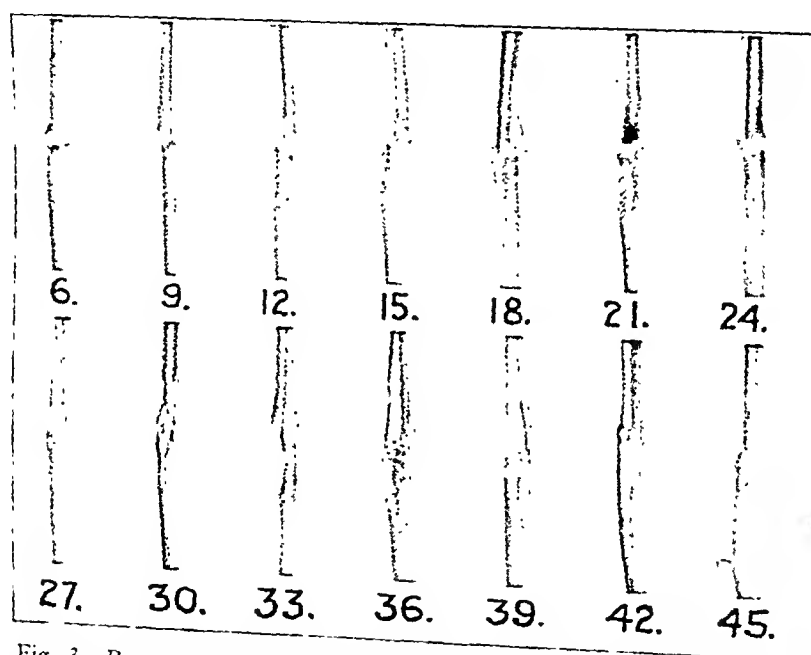


Fig. 3—Roentgenograms of typical fractures at three day intervals from the sixth to the forty-fifth postoperative day. The animals were fed the standard diet. Note the haziness of the ends of the fractured fragments after the thirtieth day.

left fibula only after the twenty-seventh day, while in the standard curve parallelism of the ratios was present practically throughout.

Studies of the roentgenograms of the calluses of the animals fed on the diet high in protein showed that the ends of the fractured fragments could be identified as separate entities for a much longer period than they could be in the controls (figs. 3 and 4). Gross examination of the calluses also revealed the same persistency of the identity of the

7. Subsequent work since this article was submitted for publication has shown that after the forty-fifth day there is again a period when the breaks occur at the site of fracture.

fragments in the bones of animals fed on the diet rich in casein. The measurements of the external diameters of the calluses were practically the same for both groups.

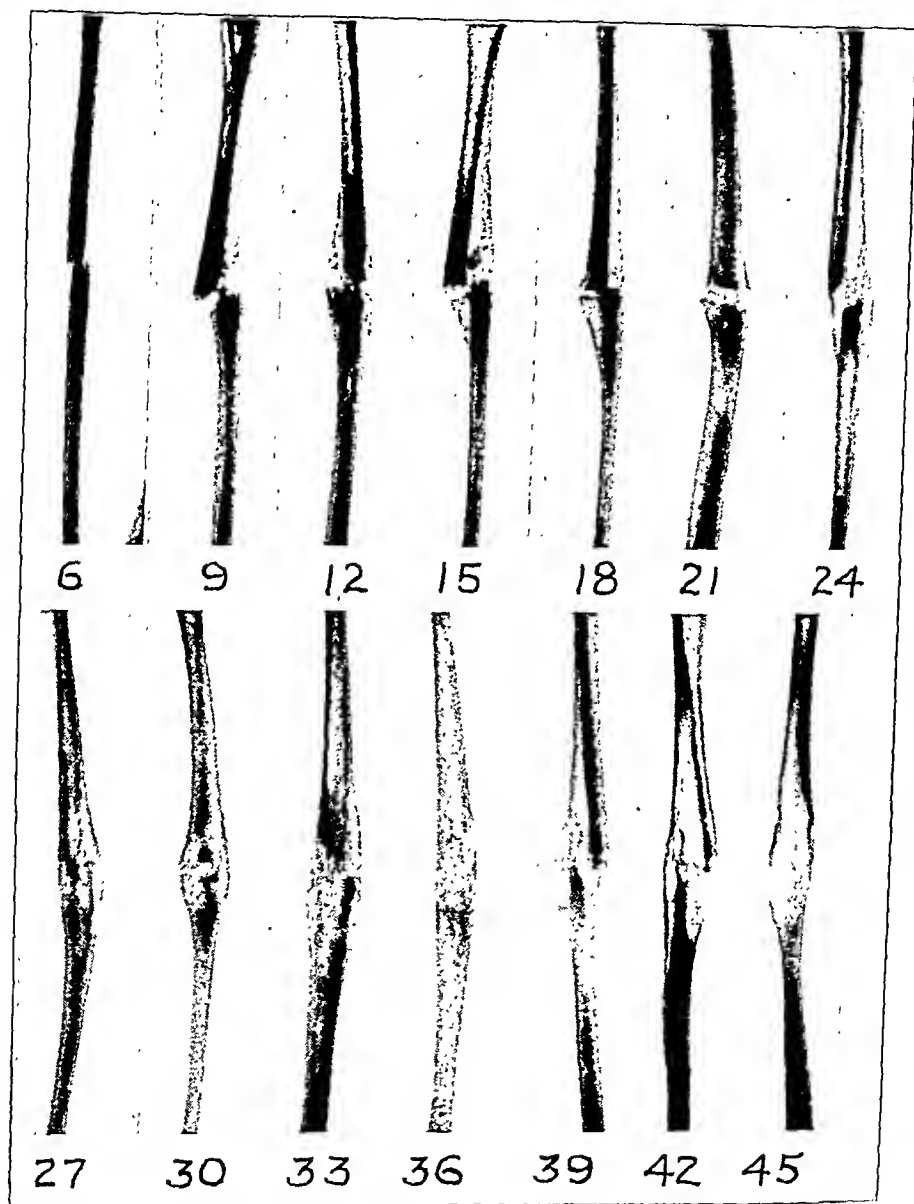


Fig. 4.—Roentgenograms of typical fractures of animals fed a diet rich in casein. Note the distinctness of the ends of the fractured fragments even until the forty-second day.

#### COMMENT

The data suggest that a diet rich in casein strengthens normal bone and speeds the healing fractures. Our first thought in using this diet was that the increase in the amount of casein simply increased the

protein content of the diet. However, it soon became apparent that increasing the casein also increased the salt and vitamin content of the diet. The animals were therefore ingesting a greater quantity of three elements which could strengthen bone and hasten healing. All three would also provide greater availability of the calcium salts. That there was greater availability of the calcium salts is attested by the increase in strength of the normal fibulas and the more rapid rate of healing. In addition, there was some substantiation for the greater availability of calcium salts found in the behavior of the fractured fragments. Axhausen<sup>8</sup> believed that the absorption of the ends of the fractured fragments during healing made available a local source of calcium. On the diet rich in casein this absorption was not so apparent either by gross or by roentgen examination, suggesting that the calcium obtained from the fragments was not needed.

Not all of the rapidity of the initial rise of the curve of healing on the diet rich in casein can be attributed to the greater availability of calcium salts, however. Part of it undoubtedly must be from the stimulation of fibrous proliferation by the diet high in protein. Harvey and Howes<sup>9</sup> have shown that wounds of soft tissues have a greater rate of fibroplasia on a diet high in protein. This stimulation alone might account for the changed contour of the first two periods of the curve.

#### CONCLUSIONS

1. A diet rich in casein increased the strength of bone per unit of body weight in rats.
2. A diet rich in casein accelerated the rate of healing of fractures.

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8. Axhausen: *Verhandl. d. deutsch. path. Gesellsch.* 16:309, 1913.

9. Harvey, S. C., and Howes, E. L.: *Ann. Surg.* 91:641 (May) 1930.

## TREATMENT OF VARICOSITIES

### PRELIMINARY HIGH LIGATION OF THE INTERNAL SAPHENOUS VEIN WITH THE INJECTION OF SCLEROSING SOLUTIONS

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In December 1928 the clinic for peripheral vascular conditions was organized at the Massachusetts General Hospital to study and direct the treatment of varicose veins and other circulatory disturbances of the extremities. Since the inception of the clinic the care of patients admitted to the hospital as well as those seen only in our outpatient department has been under the supervision of the same group of men, and thus my associates and I have been able to maintain a desirable degree of unity in the different phases of the work. By an interchange of individual ideas during the combined weekly house visit, when all of the members of the clinic are present, and by seeing for ourselves every patient who reports to the outpatient department, we have a favorable means of determining the outcome for all of the patients treated, whether they have been hospitalized or not. From the disappointing results of our earlier work in the treatment of varicose veins by the injection method alone<sup>1</sup> it was felt that the question of the efficacy, in certain cases, of combining preliminary high ligation of the internal saphenous vein with injections was a matter worthy of further study. The following report is based on our experience during the period from August 1931 to April 1933 in treating one hundred and seventeen patients by the combined method of ligation and injection. All of the members of our clinic have contributed suggestions as to methods of procedure and have participated in the actual work involved in caring for the patients, and the technic and principles set forth in the following pages represent the combined efforts of a group rather than the effort of any one person.

In many cases of varicose veins of the internal saphenous system it can be demonstrated that with the patient in the upright position the blood flow in the main trunk is reversed and the lower part of the leg subjected not only to the weight of this column of blood but to any increased intra-abdominal venous pressure occasioned by exertion, straining and similar forces. So clearly and convincingly was this fact

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From the clinic for peripheral vascular conditions, Massachusetts General Hospital.

1. Faxon, H. H.: End Results in the Injection Treatment of Varicose Veins, *New England J. Med.* 208:357, 1933.

stated by Trendelenburg<sup>2</sup> that his work has remained a classic corroboration of an underlying principle which was recognized years before his time. Subsequent work with roentgenograms and injections of iodized poppy-seed oil<sup>3</sup> and direct manometer readings<sup>4</sup> have added so little that the Trendelenburg test is still our best guide for determining the competency of the valves in the main saphenous trunk above the knee. It would seem worth while to restate briefly the salient points of the test, as an understanding of its basic principles are of the first importance in any treatment of varicose veins.

The Trendelenburg test (fig. 1) is carried out by elevating the affected leg as the patient lies on the examining table to an angle of 45 degrees, thus essentially emptying the varicosities of blood. A tourniquet is then placed about the thigh

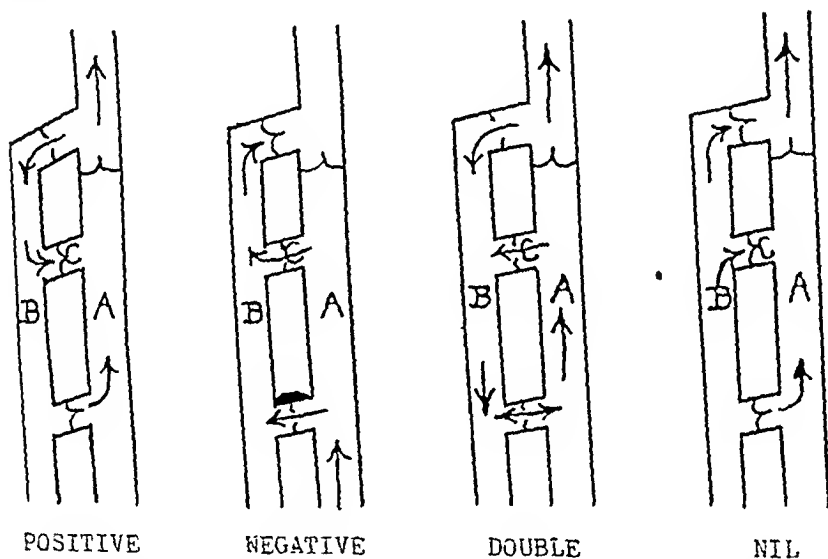


Fig. 1.—The four Trendelenburg states, according to Bernstein (*Acta chir. Scandinav.* 62:66, 1927), as modified by McPheeters ("Varicose Veins," Philadelphia, F. A. Davis Company, 1931). A indicates the femoral vein; B, the internal saphenous vein, and C, the communicating vein.

tight enough to constrict only the superficial venous circulation, and the patient is allowed to stand with the tourniquet still in place. If the varicosities fill rapidly (i. e., within one-half minute) from below, incompetence of the valves in the branches communicating with the deep system is signified. A slow filling or no filling under these conditions means that the adequate functioning of the valves

2. Trendelenburg, F.: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen, *Beitr. z. clin. Chir.* 7:195, 1891.

3. McPheeters, H. O., and Rice, C. O.: Varicose Veins: Circulation and Direction of the Venous Flow, *Surg., Gynec. & Obst.* 49:29, 1929.

4. de Takáts, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: Impairment of Circulation in the Varicose Extremity, *Arch. Surg.* 8:671 (Feb.) 1929. McPheeters, H. O.; Merkert, C. E., and Lundblad, R. A.: The Mechanics of the Reverse Flow of Blood in Varicose Veins as Proved by Blood Pressure Readings, *Surg., Gynec. & Obst.* 55:298, 1932.

is little, if at all, impaired. If the tourniquet is released with the patient still standing and a prompt engorgement of the internal saphenous trunk and its superficial branches ensues, it is evident that the valves in the main trunk of this system are incompetent to withstand the back pressure to which they are subjected. With incompetent valves in the communicating branches and the main trunk, filling occurs from below and is augmented from above when the constriction about the thigh is removed. From a study of the distribution of the prominent veins of the leg and a repetition of the test with the tourniquet applied a second time just below the popliteal space, varicosities of the external saphenous vein alone or a combination of a varicose condition involving the external and internal systems may be properly evaluated.

With an understanding of the facts brought out by this test it is obvious that any effective treatment of varicosities of the internal saphenous system in which incompetence of the valves in the main trunk can be demonstrated must include some step to shut off the reverse flow of blood into this system. Trendelenburg<sup>2</sup> sought to secure this end by ligating the main saphenous trunk and recommended that this be done at the junction of the middle and lower thirds of the thigh. Later workers, including Mayo,<sup>5</sup> Miller<sup>6</sup> and Homans,<sup>7</sup> rightly felt that a higher point of ligation than that used by Trendelenburg would more effectively forestall recurrences by also removing from the upper portion of the main trunk the back pressure to which the entire system had been subjected. They further pointed out the fallacy of believing that by simple ligation the varicosities could be corrected, and they sought by surgical excision of the offending veins to supplement the benefits attributable to ligation alone. Because of the greater thoroughness and safety of the injection method of treatment, we feel that following high ligation it is better in all save the exceptional case to obliterate the varicosities by injecting sclerosing solutions than by resorting to the old surgical method of excision. It must not be forgotten in the stress that is here laid on high ligation in selected cases that this important operative step must be combined with an effective, thorough and complete subsequent course of treatments by injection if satisfactory results are to be secured.

With the advent of enthusiasm for the treatment of varicose veins by injection a lamentable disregard for underlying considerations soon became apparent, and although the chief sponsors for the use of sclerosing solutions recommended making injections into the main trunk as high in the thigh as it could be made out, many less experienced workers were hesitant in making injections above the knee, and still

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5. Mayo, C. J.: *Treatment of Varicose Veins*, Surg., Gynec. & Obst. **2**:385, 1906.

6. Miller, R. T., Jr.: *The Results of Operative Treatment of Varicose Veins of the Leg by the Methods of Trendelenburg and Schede*, Bull. Johns Hopkins Hosp. **17**:289, 1906.

7. Homans, John: *The Operative Treatment of Varicose Veins and Ulcers, Based on a Classification of These Lesions*, Surg., Gynec. & Obst. **22**:143, 1916.

others employed ineffective measures to determine the presence of the main trunk in the thigh. Still more important was the question of the permanence of the artificially produced occluding thrombus in the upper portion of the internal saphenous vein. It seems reasonable to suppose that the tendency to recanalization is greater in the all-important thrombosed upper portion of this vein, where the region is still subject to a certain degree of back pressure, than in the smaller thrombosed branches of the lower part of the leg, where the factor of back pressure had been eliminated. From a practical point of view, our microscopic studies of thrombosed veins and those by de Takáts and Quint,<sup>8</sup> McPheeters and Lufkin<sup>9</sup> and Ochsner and Garside<sup>10</sup> show that recanalization occurs, and the clinical results obtained in the clinic for peripheral vascular conditions of the Massachusetts General Hospital<sup>1</sup> and by Howard and his associates<sup>11</sup> have disappointingly reminded us of the efficacy of nature in reestablishing a lumen in an apparently successfully obliterated vein.

On the basis of the statistical study of our end-results with three hundred and fourteen patients treated by the injection method alone,<sup>1</sup> I believe that 29.3 per cent represents the minimum number of cases in which high ligation is necessary. The proportion of the total number of cases showing marked varicosities is higher and the need for ligation greater in a clinic such as ours than it is among patients who come to a doctor's office for private treatment. The feeling of all of us connected with this work at the Massachusetts General Hospital since the aforementioned statistical study was compiled has been increasingly in favor of preliminary operation. With more careful examination than we at first employed to determine whether or not the main saphenous trunk above the knee is varicosed, we have come to the belief that undoubtedly more, rather than less, than 30 per cent of our cases present at entry our stipulated indications for primary ligation.

Moszkowicz,<sup>12</sup> de Takáts<sup>13</sup> and others have advocated high ligation of the main internal saphenous vein in cases in which the valves in the

8. de Takáts, G., and Quint, H.: The Injection Treatment of Varicose Veins, *Surg., Gynec. & Obst.* 50:545, 1930.

9. McPheeters, H. O., and Lufkin, N. H.: Pathological Studies on Injected Varicose Veins, *Surg., Gynec. & Obst.* 54:511, 1932.

10. Ochsner, A., and Garside, E.: The Intravenous Injection of Sclerosing Substances, *Ann. Surg.* 96:691, 1932.

11. Howard, N. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: Study of Pathologic Nature of Recurrence and Critical Survey of Injection Method, *Arch. Surg.* 22:352 (March) 1931.

12. Moszkowicz, L.: Behandlung der Krampfadern mit Zuckerinjektionen kombiniert mit Venenligatur, *Zentralbl. f. Chir.* 54:1732 (July 9) 1927.

13. (a) de Takáts, G.: Ambulatory Ligation of the Saphenous Vein, *J. A. M. A.* 94:1194 (April 19) 1930. (b) de Takáts, G., and Quillin, L.: Ligation of the Saphenous Vein, Report on Two Hundred Ambulatory Operations, *Arch. Surg.* 26:72 (Jan.) 1933.



main trunk are shown to be incompetent, as a preliminary step in carrying out the injection method of treatment. However, in reviewing the literature on this subject one is impressed with two facts which are so startling in the light of our experience at the Massachusetts General Hospital as to make it seem worth while to explain in detail our feelings on these points.

In the first place, the importance of dividing the saphenous vein above its highest branches and at the point where it empties into the femoral vein is mentioned frequently but rarely stressed. We feel with Homans<sup>14</sup> that to relieve back pressure completely and finally the great saphenous vein must be ligated at its entrance into the femoral vein in the groin. If a stump of the saphenous vein is left, which includes the remarkably constant three highest tributaries of this vein, namely, the superficial iliac circumflex, the superficial epigastric and the superficial external pudendal veins (all of which branch off within the first 3 cm. as a rule), the permanent success of the operative procedure is seriously jeopardized. This is true because these branches will in time yield to the added thrust of back pressure on them, which ligation at a level below their junction with the main trunk occasions, and through their collaterals varicose channels will again be established in the leg. The patient pictured in figure 2 underwent ligation in our clinic before we fully appreciated the importance of ligation at the saphenofemoral junction, and within a year the new varicosities on the front of the thigh, which had been established through their collaterals with the three highest saphenous branches, were apparent and of good size. Furthermore, with high ligation as we carry it out, there is no patent upper stump of saphenous vein left in which thrombosis can occur and inadvertently become dislodged. Thus the danger of emboli, although not eliminated, is, we believe, materially reduced.

In the second place, from reading most of the articles one is left with the impression that ligation of the main trunk of the saphenous vein is a trivial affair. We should be the first to agree if one spoke of isolating the main trunk at a convenient point well below the crease in the groin or at one of the lower points of prominence of the vein, and we do not mean to convey the impression that as we carry out the procedure it is a complicated operation. We do feel, however, that to ligate the vein in the fossa ovalis and thus insure a permanently effective dam against the back pressure on the veins in the lower part of the leg is not the simplest of procedures. It is all-important that the dissection should not traumatize surrounding structures, that adequate surgical preparation is carried out, and that a completely aseptic technic is maintained. Failure to locate the vein accurately gives rise to unnecessary

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14. (a) Homans, J.: The Operative Treatment of Varicose Veins, Varicose Ulcers and Phlebitis, *New England J. Med.* 200:965 (May 9) 1929; (b) Homans.<sup>7</sup>

injury to the lymphatics and the opening up of "dead space" in the subcutaneous tissue, while roughness in handling the vein itself may result in hemorrhage of serious proportions from the upper end of the saphenous or the femoral vein.

#### TECHNIC OF EXAMINATION

We believe that a complete physical examination of every patient on whom an operation is to be performed is so obviously a sound procedure as to need no

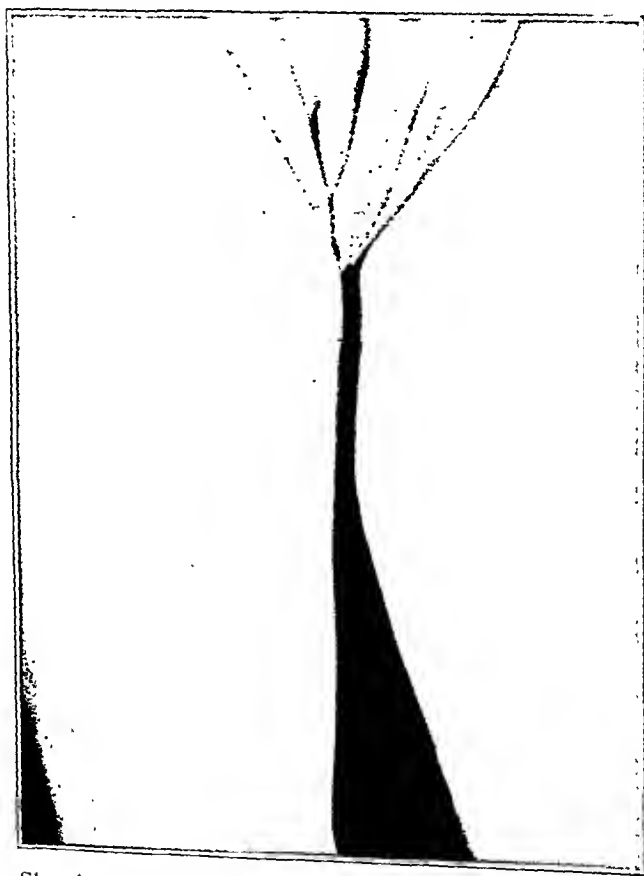


Fig. 2.—Showing recurrences ten months after too low a ligation of the main saphenous trunk had been carried out. A second ligation, through an incision at least 2 inches (5 cm.) above the old scar shown in the photograph, was made according to the technic described in the text. At this time it could be demonstrated that the recurrences were due to the patent stump of the internal saphenous vein with its three highest branches, which had persisted because of the improperly executed first operation.

explanatory defense. When ulcers of the lower part of the leg are present, the laboratory studies should include a urinalysis, a Wassermann test of the blood and cultures taken from the ulcerous area. The detailed examination of the lower extremities should be primarily concerned with ascertaining the adequacy of the arterial circulation by invariably palpating for pulsations in the dorsalis pedis and

posterior tibial arteries, by excluding symptomatic orthopedic abnormalities and by employing all measures which would help in evaluating the problem that the varicosities themselves present. These measures include Homans'<sup>15</sup> modification of the Schwartz test, that of percussing the varicose main trunk below the knee and determining whether the impulse is conveyed up the vein to the fingers of the other hand, which are firmly pressed over the fossa ovalis. Often when no main trunk of the internal saphenous vein can be seen or made out by the usual methods of palpation, this procedure will be found to be of the greatest assistance in revealing the presence of a large varicosed main trunk. We have also employed the Schwartz test as originally described by Chevrier,<sup>16</sup> which consists in percussing the vein with the fingers of the upper hand. If an impulse can be seen or felt at the knee, it points directly to incompetence of the valves in the intervening portion of the vein. The Trendelenburg test as outlined earlier should always be carried out, and also the von Perthes modification of the test. The modification is used to determine the status of the deep venous circulation, and in cases in which there is a history of old phlebitis it is the easiest method of ascertaining whether or not the varicosities have taken over the burden of acting as the chief means of return of blood from the leg to compensate for previous impairment of the deep venous return. This modification is carried out by having the patient walk about with the tourniquet applied as previously described. If the varicosities become more prominent, the deep veins have been injured by the old phlebitis, and any treatment of them is contraindicated, whereas, if the reverse is true, ligation may be done. The presence and extent of an acute phlebitis, the degree of edema and the size and location of the ulcerations should be carefully noted. As the only effective method of keeping a record of the case, the findings should be entered on a diagrammatic chart of the legs.

#### INDICATIONS FOR LIGATION

We believe, except as noted under contraindications cited later, that in all cases of varicosities in which the main trunk of the saphenous vein in the thigh is shown to have incompetent valves primary high ligation should be performed in the thigh before injections are carried out in the lower varicosities. Some patients of advanced age in this group were treated conservatively with bandages or local injections into the chief offending veins because their general life expectancy and relative absence of symptoms did not seem to justify the more extensive procedure. Certain other patients with incompetent valves in the main trunk refused to undergo primary high ligation and received treatment by injection, alone, despite our expressed opinion that the results would almost surely be temporary. If both sides present the stipulated indications for operation, bilateral ligation may be done at the same operation. In fifty-eight cases, or 49.5 per cent of our series of one hundred and seventeen cases, the bilateral procedure was carried out.

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15. Homans, J.: *Varicose Veins and Ulcer: Methods of Diagnosis and Treatment*, Boston M. & S. J. 187:258 (Aug.) 1922.

16. Chevrier, L.: *De l'examen du reflux veineux dans les varices superficielles*, Arch. gén. de chir. 1:45, 1908.

## CONTRAINDICATIONS TO LIGATION

We recognize four definite contraindications to high ligation of the internal saphenous vein:

1. That the varicosities are compensatory, as shown by the aforementioned von Perthes test, is definite evidence that no form of treatment should be instituted.

2. The presence of a superficial or deep acute inflammatory process in the groin is a definite reason for delaying the operation until the process has completely subsided. Sufficient time must have elapsed following its recovery (depending on the nature and extent of the inflammation) to make sure that surgical intervention will not cause a flaring up of the old trouble.

3. The occurrence of hemolytic streptococcus organisms in varicose ulcers makes ligation unwise until the infection has been cleared up. We have had three instances in our series of one hundred and seventy-five ligations in which secondary inflammation of the wound in the groin would seem to have been attributable to the virulent organisms present in the ulcer. We felt in these cases that it was our trauma to the potentially involved lymphatics in the groin that gave rise to this trouble. With the use of dressings saturated with surgical solution of chlorinated soda and rest in bed these organisms can usually be eliminated, as shown by repeated cultures of the ulcer. If at first we fail to rid the area of them, temporary measures are taken in the treatment of the ulcer and veins until the virulent organisms can be shown to have disappeared.

The presence of an acute superficial phlebitis of the lower part of the leg or an extensive inflammatory reaction about an ulceration is not a final deterrent in proceeding with high ligation. In these cases, however, of which we have had three in our series, we have treated the patient conservatively with rest in bed, hot moist applications and the like for a period of from three days to a week before operation. In selected cases of acute superficial phlebitis which does not involve the upper half of the thigh, we believe with Homans<sup>14a</sup> that by high interruption of the main saphenous trunk we lessen the danger of extension of the process into the pelvic veins, shorten the period of convalescence and reduce the risk of pulmonary emboli. However, we have consistently been opposed to making injections into veins that have shared in an acute phlebitic process until at least six months after the inflammation has completely subsided.

4. The treatment of a patient temporarily confined to bed is in our minds not justified, as we feel with de Takáts<sup>15a</sup> that the act of walking following operation is not only a convenience to the patient, but, more important, a safeguard against the formation of untoward thromboses

and the occurrence of emboli. We have been requested frequently at the hospital to carry out high ligations on patients temporarily confined to bed from some other operation or to combine our procedure with other operative measures. We have refused to do this, preferring to wait, for the aforementioned reasons, until the patient is ambulatory.

#### TECHNIC

There has never been any doubt in our minds as to the advisability of hospitalizing the patients for a period ordinarily including two nights and part of three days. We believe that it is important that the patient enter the hospital the night before operation, as an adequate preparation of the field is indispensable and should be carried out with the same thoroughness as for a laparotomy. The groin is a region subject to the most indifferent hygienic care by many patients, and in obese persons who show an outstanding lack of cleanliness in the region of the groin two days are necessary to prepare the patient properly for operation. Our preoperative preparation includes shaving the pubic hair and its extension into the groin, thoroughly cleansing the skin and applying a spica to hold the enveloping sterile towels in place. Any other form of final dressing invariably slips down and leaves exposed the very area one wants most to have covered. We do not make a practice of marking the location of the vein in the groin at the time of examination on entry of the patient, as we have been unable to find a stain which will not irritate the skin or wash off during the night before preparation. If the operator is not completely familiar with the location of the vein he will be greatly helped by having the patient stand beside the operating table after the sterile drapes are removed and by marking by a scratch on the skin or the application of iodine the exact location of the vein in the groin as brought out by percussing the trunk at the knee.

Ordinarily it is not necessary to order preliminary medication, but if the patient is of a nervous temperament, suitable drugs may be employed, as with any surgical procedure. If the patient is required to stand, as suggested earlier, shortly after receiving a medication of morphine he may feel momentarily a bit dizzy and should have some one beside him at the time.

The skin is prepared with tincture of metaphen, and the site of the operation is draped with sterile goods. If the ligation is to be bilateral, one side should be kept covered with a sterile towel while the other is exposed. Ordinarily the side with the most pronounced varicosities is ligated first. A separate set of instruments should be employed for each groin. The foot of the table is elevated about 10 degrees to promote the emptying of the veins during the ligation. The infiltration of the skin is carried out with 1 per cent procaine hydrochloride to which no epinephrine has been added. The line of wheals starts at a point in the deepest crease of the groin from 2 to 4 cm. below Poupart's ligament, directly over the pulsation of the femoral artery, and extends medially along this crease for a distance of 5 cm. The deeper layers are successively infiltrated, frequent traction being exerted on the plunger of the syringe to insure against injecting the procaine hydrochloride solution directly into the circulation. Starting at the medial border of the femoral artery and running parallel to and just below the crease in the groin, a skin incision from 3 to 5 cm. in length (depending on the amount of fat present) is made down to the superficial fascia, which is a well defined structure between the superficial and deep portions of which the saphenous vein lies, surrounded by a considerable amount of loose areolar tissue and fat (fig. 3, A).

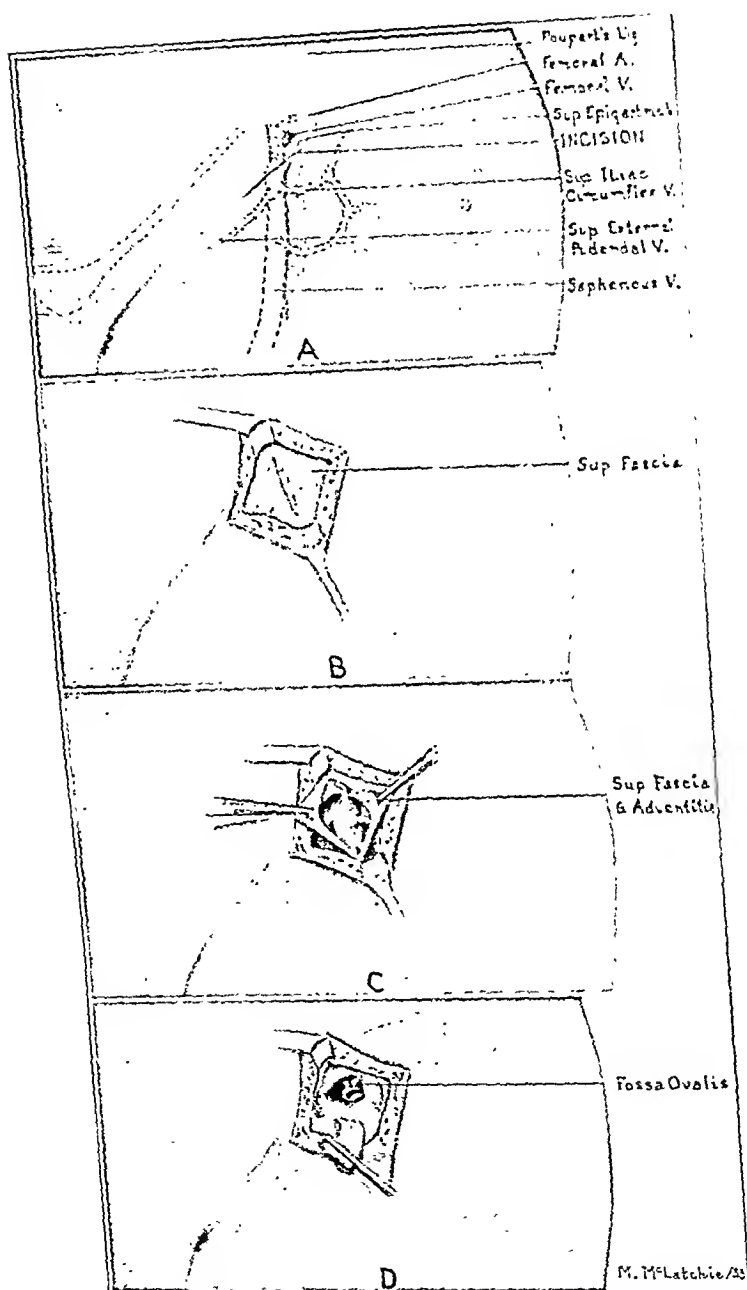


Fig. 3.—Drawings illustrating the operative steps for high ligation of the internal saphenous vein. The details of the procedure are described in the text under the heading "Technic."

The mistake is frequently made in obese persons of seeking the vein in the subcutaneous fat above the layer of superficial fascia before the operator realizes that he has occasioned a certain amount of unnecessary trauma by not proceeding deeply enough with the dissection.

With retraction at the upper and lower margins of the wound, the superficial fascia with its associated underlying areolar tissue is vertically incised, and the saphenous vein found to be directly beneath (fig. 3, *B*). If the operator is uncertain of his landmarks, a transverse incision instead of a vertical incision through this fascia will facilitate the location of the vein. The adventitia, which is made up of a number of layers, is carefully picked up with forceps at the most convenient central portion of the wound and incised in a vertical direction over a distance of 1 cm. The dissection should be carried down to the natural line of cleavage formed by the smooth underlying surface of the vein. When this is reached, the layers comprising the adventitia, with those of the already incised superficial fascia, are grasped on both sides by hemostats, and the incision in the adventitia is carried up and down to give adequate exposure (fig. 3, *C*). This step helps tremendously in the subsequent freeing of the vein and its highest branches. At this stage a curved half-length can be readily passed beneath the vein, which is clamped with two straight hemostats 1 cm. apart. The main trunk is divided midway between the clamps to facilitate the isolation of the upper end and the exposition of its branches. These latter, of which there are always at least the three already mentioned, are separately snapped, divided and directly tied off to keep the field of operation as free as possible from encumbering instruments. The upper end of the internal saphenous vein is exposed as it dips through the fossa ovalis until its point of junction with the femoral vein can be made out. A no. 2 chromic catgut ligature is placed just distal to this point to prevent puckering of the femoral vein, and a second tie, 0.5 cm. distal to the first, is used as an added reinforcement. The upper segment of the vein is again divided just below the second tie in order to remove the portion traumatized by the upper hemostat (fig. 3, *D*).

It has seemed reasonable to us to attempt obliteration by retrograde injection at the time of operation of at least a portion of the saphenous vein in the thigh, as suggested by Moszkowicz.<sup>12</sup> Before the wound is closed, the edges of the end of the vein showing above the hemostat are grasped on both sides; the clamp is removed and the cannula (fig. 4), devised by the author to fit a vein of any size, is tied in position. The leakage of blood through the cannula while one is waiting for the syringe of the sclerosing solution may be prevented by angulating the vein forward over the lower edge of the superficial fascia. We have used from 10 to 20 cc. of a solution of 30 per cent invert sugar and 10 per cent sodium chloride with each injection, depending on the size of the vein. By elevating the leg, pressing over the trunk in the midthigh and aspirating the blood from the vein, we have attempted at least partially to empty the vein before injections are carried out. Following the injection, the vein is tied off below the cannula, and with traction on the plunger of the syringe to prevent the escape of any of the solution into the tissues, the vein is again divided just below the cannula and above this last placed tie. The wound is flushed out with salt solution; the edges of the superficial fascia are brought together with one or two plain catgut sutures to obliterate any "dead space" and the skin is closed with interrupted silk stitches. A small square of gauze is held in place by a piece of adhesive tape in which an air

vent has been cut to serve as a dressing, and Bender bandages are applied to the lower parts of the legs.

*After-Care.*—We believe that the patient should be forced to a certain extent to be ambulatory following the operation in order that the muscles of the leg by their pumping action in walking may help to dissipate any sluggishness in the venous return and so reduce the likelihood of untoward thromboses and emboli. To that end we have the patients walk a few steps from the operating room truck to their beds following ligation and then accord them lavatory privileges so that at intervals they may be active. It is a mistake to feel that there is no significant difference between having the patients ambulatory after operation and merely having them out of bed in a chair. The former is to be encouraged as of definite benefit to them, whereas the latter is to be condemned, since, with the passive dependence of the lower extremities, venous stagnation is actually increased. When the patient has returned from the operating room, the foot of the bed is

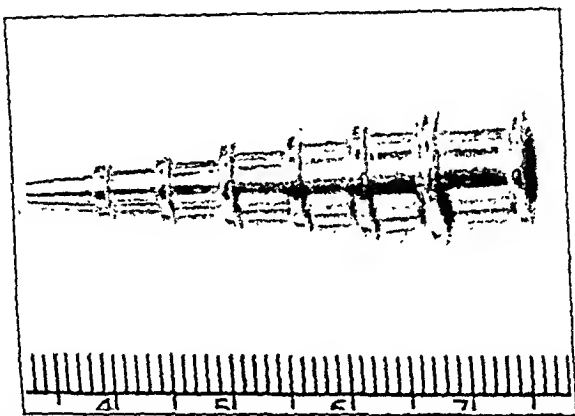


Fig. 4.—The cannula used for the retrograde injection of a sclerosing solution into the distal end of the vein at the time of operation.

elevated on a chair with the same idea in mind of aiding venous return in the legs. Following ligation, the wounds in the groin give little discomfort, but it is not uncommon for the area in the thigh into which injections have been made to show the somewhat uncomfortable reaction of tenderness along the course of the vein that is often associated with the use of sclerosing solutions. Barring complications, the patient, still wearing the Bender bandages below the knee, leaves the hospital the day following the operation, but he is instructed to avoid strenuous exertion during the following week. The stitches are removed on the fifth or sixth day, and all dressings are abandoned a day or so later.

The course of treatments by injection is started as soon as the wound is healed and may be carried out according to the operator's method of choice so long as the final result is a firm thrombosis of every varix that can be detected by inspection or palpation. Fewer visits (usually from three to five) are required in cases of injections following the preliminary operative step than in cases in which there is no preliminary operation. This is due to the fact that by high ligation and retrograde injection not only is the upper portion of the saphenous system thrombosed, but the remaining varicosities (relieved of the back pressure formerly



exerted on them) are less distended and less prone to show "excessive reactions" and respond over a greater extent to each injection than in the cases in which operation has not been performed.

### COMPLICATIONS

The procedure may be followed by certain complications which contribute largely to our feeling that the operation is definitely not without its risks. The most serious untoward event is postoperative pulmonary emboli.

In the series of one hundred and seventeen cases we have not seen this complication, but since these figures were compiled we have had one fatality from a postoperative pulmonary embolus following ligation of the veins. The details of this case are significant, owing to the fact that through faulty liaison between the members of our clinic and the resident surgeons in the hospital, many of the principles we have advocated were not followed out in this instance. We believe that the complication might possibly have been avoided had our technic been carefully followed. Feeling that the experience with this patient substantiates the importance of closely adhering to our stipulated rules for operation, the salient features of the history, with certain explanatory comments, are given in the following paragraphs.

### REPORT OF A CASE

An extremely obese white woman, aged 54, entered the hospital on the recommendation of the outpatient surgeon in our clinic because of bilateral varicose veins which had been present for ten years and were becoming progressively worse. They had been complicated for three months by an ulceration above the left internal malleolus. The varicosities were large; they involved only the internal saphenous system and showed incompetence of the valves in the main trunk in the thigh but essentially no impairment of the valves in the perforating branches of the lower part of the leg. There was pigmentation of the skin above the left internal malleolus with a crusted lesion 1 cm. in diameter in the same region. The ankles showed a slight amount of pitting edema which the patient had noticed off and on for several years. The peripheral arterial circulation was good, but the general circulatory condition showed a considerable degree of arteriosclerosis with a hypertension of 198 systolic and 110 diastolic and slight cardiac enlargement. The most striking feature of the marked obesity was the panniculus of fat which hung down and obscured the creases in the groins. The patient received a single preparation of the field of operation on entry, and the following day had the internal saphenous veins ligated in the groin and interrupted a second time at the level of the knee. The operator's note stated that because of the great amount of subcutaneous fat he could not demonstrate the saphenofemoral junctions. Retrograde injection into the vein on the left was carried out with 20 cc. of the sugar and salt preparation; Bender bandages were applied to the lower parts of the legs, and the foot of the bed was elevated when the patient returned to the ward. Twenty-four hours after the operation the temperature was 101 F., and there was slight tenderness at the lower incisions. On the following day the patient was allowed to sit

in a wheel-chair, and hot, moist applications were applied to the areas of induration. Two days later the wounds were opened; cultures showed a pure growth of hemolytic streptococci. The wounds improved, and the temperature returned to normal. On the eleventh postoperative day the patient suddenly presented the typical picture of a massive pulmonary embolus and died. Permission for an autopsy was refused by her family.

In retrospect, we feel that at least two days were needed to prepare the patient properly for the operation, that cultures from the crusted ulceration should have been taken and reported on before ligation was carried out, and that the patient should not have been allowed to sit passively in a wheel-chair during convalescence. The ligation should have been made at the saphenofemoral junction; the second interruption of the main saphenous trunk at the level of the knee should not have been carried out.

We have not mentioned the procedure of interrupting the main saphenous trunk a second time at the level of the knee because we feel from our experience in adopting this added operative step in 50 per cent of the ligations in this series that both the theoretical and the clinical advantages are not justified by the added risk. The wounds at the knee, as in the case cited, have shown a marked tendency to heal poorly as contrasted with those in the groin, and we no longer practice or advocate a second interruption of the main saphenous vein below the ligation in the groin.

In seven, or 5.9 per cent, of our cases a varying degree of secondary inflammation has been evident about the wound, necessitating hospitalization beyond the usual period. We feel that the reasons for this complication can be traced to faulty operative technic, contamination of the wound with the sclerosing solution or failure to observe our stipulated set of rules of contraindications.

Hemorrhage at the time of operation or later has not been a complication in any of our cases.

#### RESULTS

Our end-results in this series of cases will be determined within the next few months, so that at present we have only a strong conviction based on our untubulated subsequent observation of these patients and the findings of others<sup>17</sup> that the underlying principles we have advocated here are sound. We believe, in cases in which the valves in the main trunk above the knee can be shown to be incompetent, that the results obtained by the combination of high ligation and subsequent injections will show a definite improvement over those obtained with injections alone or with the older forms of radical surgery.

17. Moszkowicz.<sup>12</sup> de Takáts.<sup>13b</sup>

It is outside the scope of this paper to elaborate on the subject of the treatment of ulcers, varicosities of the short saphenous vein or the problems presented by incompetent valves in the communicating branches in the lower part of the leg. These must be dealt with when present, and when found, as they usually are, in conjunction with a varicose internal saphenous vein in the thigh, we believe that treatment must include high ligation in the groin.

#### SUMMARY AND CONCLUSIONS

1. In cases of varicosities of the internal saphenous system in which it can be shown that the valves in the main trunk are incompetent, ligation of the vein in the groin is an indispensable adjunct to any form of treatment, since it affords the only permanent means of relieving the varicosities of the lower part of the leg from the back pressure exerted on them from above.
2. To be effective the vein should be tied off at the saphenofemoral junction, above its three highest tributaries, which would otherwise open up collateral venous channels around the point of ligation.
3. At least 30 per cent of all of the cases seen in the clinic of the Massachusetts General Hospital present at entry indications for preliminary high ligation.
4. If virulent organisms can be demonstrated in a complicating ulcer, or if there is any inflammatory process in the groin, high ligation must be postponed until these conditions have completely subsided under conservative treatment.
5. Patients on whom preliminary high ligation has been carried out should remain ambulatory following operation.
6. The procedure requires a short period of hospitalization to insure the advantages of proper operating facilities and adequate preoperative preparation of the field of operation.
7. Retrograde injection of a sclerosing solution into the distal segment of the vein at the time of operation is of advantage in supplementing the benefits of ligation alone.
8. A thorough course of injections which, because of the preliminary ligation, will entail fewer visits by the patient must be instituted following operation if the end-results in the treatment of the veins is to be satisfactory.
9. Adherence to the technic and principles here stipulated will materially reduce the incidence of complications.

10. From our experience in one hundred and seventy-five ligations we believe that the combination of high ligation and subsequent injections in cases in which the valves of the main trunk are incompetent offers a better chance of permanent cure than any other method of treatment, including the old extensive surgical procedures.

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# AVERTIN IN PREANESTHETIC MEDICATION

A SURVEY OF 1,831 SURGICAL ANESTHESIAS

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During a survey of the use of avertin in the general surgical service since 1930, certain points were noted which when correlated with known reactions to avertin were deemed of sufficient interest to merit publication. The number of cases in which avertin was used and their general distribution as to types of surgical procedures are considered sufficient to permit a comparison of the influence of age and sex on the response to a range of doses, as well as of the adaptability of this substance for different types of surgical procedures and for use with different supplementary anesthetics. This report also permits a direct comparison of the relative premedication values of two entirely different types of hypnotics, i. e., avertin (tribromethyl alcohol) and pentobarbital sodium (sodium ethyl [1-methyl-butyl] malonyl urea) used for similar purposes in the same surgical service. The report on pentobarbital sodium will appear separately.

The age range of the patients, the nature and frequency of the surgical procedures, the doses of avertin and the anesthetic supplements used are shown in table 1.

## PROCEDURES

During the evening preceding the day of operation apprehensive patients received a sedative (usually of the barbital type) in order to assure a restful preoperative night. However, 80 per cent of the group required no medication. In addition, the colon was cleansed by a warm enema. On the following morning from thirty to sixty minutes before the scheduled operation, morphine ( $\frac{1}{2}$  grain [11 mg.]) and atropine ( $\frac{1}{150}$  grain [0.5 mg.]) or fractional doses of this combination as gaged by age were administered hypodermically to 88 per cent of the patients. The remainder (including the group who were to undergo operations on the brain) received either atropine alone or no supplementary premedication. Ten minutes after the injection of morphine and atropine, avertin—the dose gaged by the age, weight and general condition of the patient—was administered rectally over a five minute period as a freshly prepared, warm, 2.5 per cent aqueous solution of avertin fluid. The patients were asleep within from two to ten

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minutes after the rectal instillation had been completed and could be transported to the operating room. The administration of the supplementary anesthetic was begun from fifteen to thirty minutes after the injection of avertin.

The routine observations included pulse and respiratory rates and systolic and diastolic blood pressures before premedication and after premedication, i. e., just before the administration of the supplementary anesthetic, during the course of the operation and postoperatively on return to bed. The urine was examined for albumin, casts and cells on admittance and for several days postoperatively. Post-operative nausea, vomiting, restlessness and pulmonary complications were likewise observed. In a small selected group of cases respiratory minute volumes were recorded by means of a Bohr gas meter before and after the administration of both the narcotic and a range of doses of the hypnotic. This was done to determine the degree of respiratory depression produced by this sequence of premedication.

TABLE 1.—Distribution of 1,831 Patients as to Age, Type of Operation, Dose of Avertin and Anesthetic Supplement

Age Groups		General Surgical Groups		Anesthetic Supplement Groups		Avertin Fluid Groups	
Years	Per Cent of Total No. of Patients	Operative Region	No. of Patients	Nature of Supplement	Per Cent of Total No. of Patients	Dose, Mg. per Kg.	Per Cent of Total No. of Patients
4 or less	5.88	Head.....	78	None.....	5.51	55 to 50..	3.09
7 to 10..	6.80	Face.....	38	Local.....	4.90	60.....	8.57
11 to 20..	14.84	Nose.....	78	Ether.....	7.20	70.....	9.57
21 to 45..	54.03	Neck.....	156	Nitrous oxide and oxygen...	27.90	80.....	32.82
46 to 65..	16.55	Chest.....	7	Nitrous oxide, oxygen and ether.....	54.40	90.....	23.64
		Breast.....	56			100.....	20.00
		Back.....	26				
		Abdomen....	310				
		Pelvis.....	631				
		Extremities..	504				
		Transfusion.	5				
		Dressing.....	11				

Initially the observations were tabulated according to the doses of avertin and subdivided according to the types of surgical procedures, irrespective of the supplementary anesthetics used. The data thus obtained were analyzed, but a regrouping of the original observations according to the types of supplementary anesthetics and subdividing according to the doses of avertin yielded simpler and equally satisfactory data and will therefore be used in this presentation.

Four surgical groups, including patients subjected to operations on the thyroid gland, gallbladder and brain and gynecological operations, differed so significantly in their reactions to anesthesia and during the postoperative period as indicated by the first analysis that these four groups have been studied separately. The reactions of the remainder of the 585 patients on whom detailed studies were made were so similar that the observations are massed and the data presented as medians in a general tabulation including an age range of from 19 to 60 years (chart 1) and smaller subdivisions (chart 2) including young (from

1½ to 18 years), intermediate (from 19 to 39 years) and older patients (40 or more years of age).

The anesthetic supplement used, except in the special surgical groups, was adapted to the patient according to the judgment of the surgeon, but no routine or fixed procedures were established. A nitrous oxide, oxygen and ether supplement was used most frequently (in 55 per cent of the entire series) and represents the anesthetic of choice.

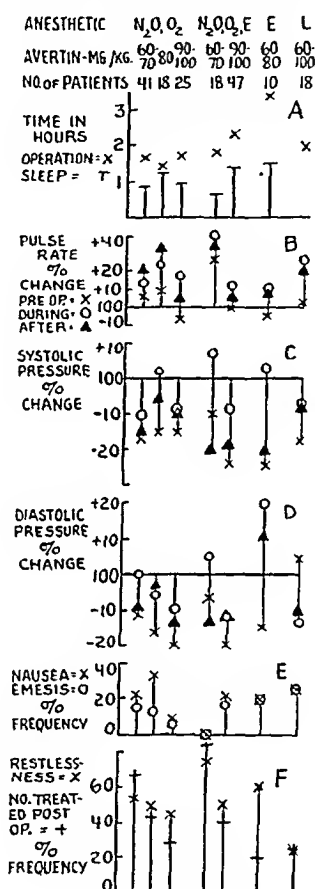


Chart 1.—The data massed according to the anesthetic supplements that were used.

In all the charts the symbols N<sub>2</sub>O, O<sub>2</sub> N<sub>2</sub>O, O<sub>2</sub>, F E and L at the top represent the anesthetic supplements nitrous oxide and oxygen, nitrous oxide, oxygen and ether, ether and a local anesthetic; the numbers in the second line, the milligrams of avertin administered per kilogram of body weight, and those in the third line, the number of patients whose anesthetic records are tabulated below.

#### OBSERVATIONS BEFORE OPERATION

*Condition of the Patient on Arrival at the Operating Room.*—Ninety-two per cent of the patients were asleep on arrival, usually well relaxed and satisfactorily analgesic. Occasionally with doses of 70 mg. or less of avertin per kilogram of body weight patients moved slightly on

arrival, but this was much more frequent after doses of from 50 to 60 mg. In general, the reactions on being moved were unimportant, but were observed in the presence of painful stimuli, irrespective of the dose administered.

*Respiration.*—The respiratory rate was either unchanged or increased slightly by premedication. As a rule, however, oscillations of one or two respirations on either side of the normal rate occurred.

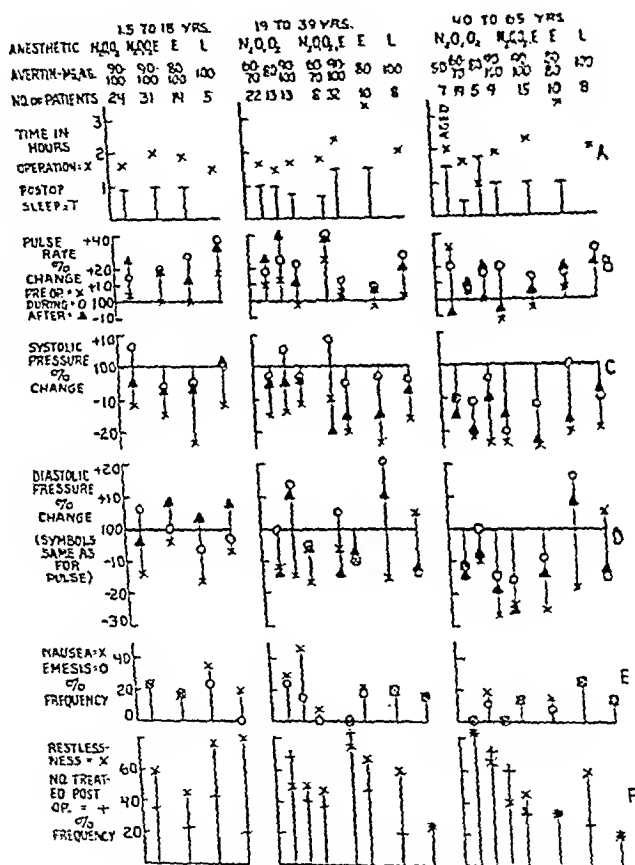


Chart 2.—The data massed according to the ages of the patients.

Occasionally following medication with heavy doses of the hypnotic or even with moderate doses in sensitive persons a significant respiratory depression was observed. Under such conditions the rate was increased and the volume decreased. Depression of the minute volume occurred with all doses. Morphine in the dose used ( $\frac{1}{6}$  grain) depressed the minute volume approximately 5 per cent. The net depression due to avertin in doses of from 80 to 100 mg. per kilogram of body weight varied from 30 to 50 per cent. One patient medicated with morphine ( $\frac{1}{6}$  grain) and 90 mg. of avertin per kilogram showed a decrease of



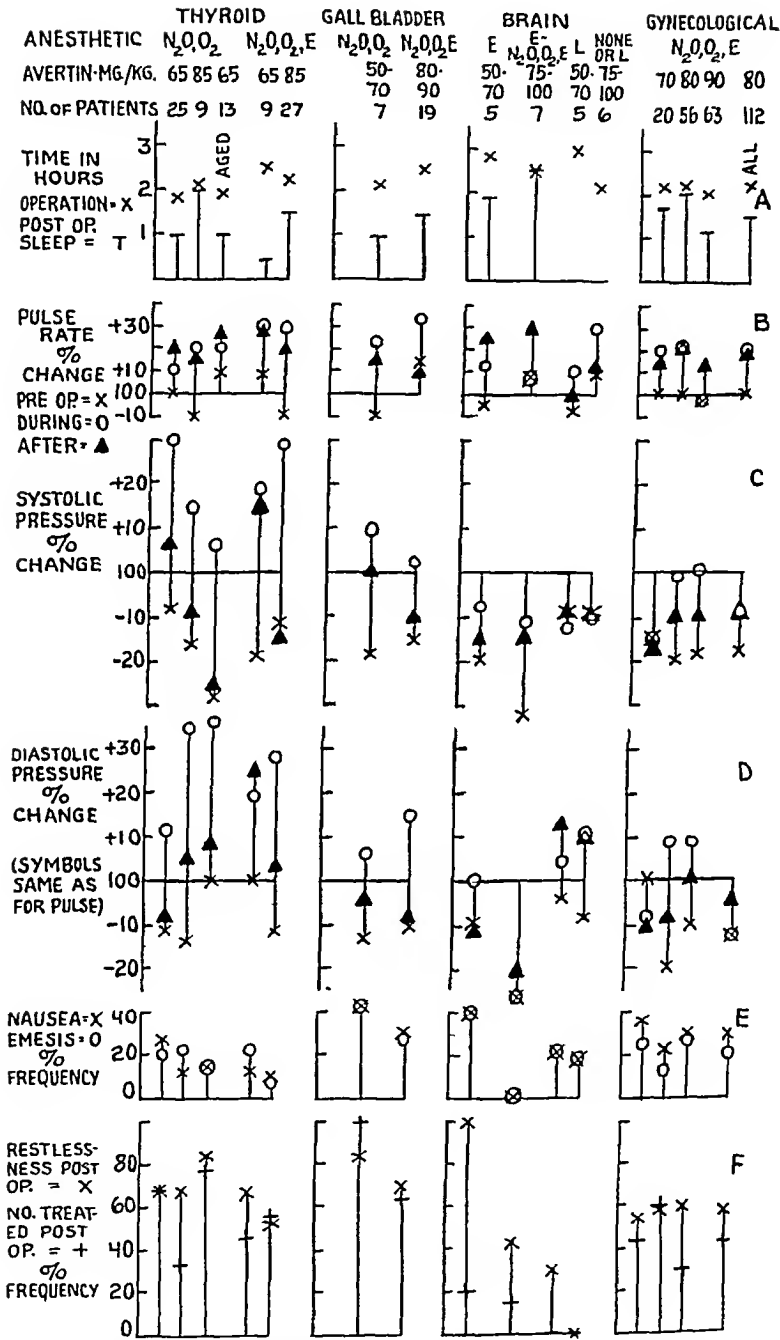


Chart 3.—The data on four special surgical groups, massed according to the types of surgical procedures involved.

70 per cent in the minute volume. The degree of depression was grossly proportional to the dose administered. With a dose of 70 mg., the minute volume diminished from 22 to 29 per cent.

*Pulse Rate.*—The preoperative pulse (indicated by the symbol  $\lambda$  in charts 1, 2 and 3, part B) was irregular and was unchanged, increased from 5 to 25 per cent or decreased from 2 to 10 per cent. The median change with doses of 70 mg. per kilogram or less was a rise of from 3 to 12 per cent above the level on admittance. With larger doses the pulse was either unchanged or depressed slightly (from 3 to 6 per cent). Exceptionally the pulse varied from 12 per cent below to 18 per cent above the normal values even with doses of 100 mg. In patients less than 18 or more than 60 years of age the pulse rate was the least stable and reacted the most variably. Differences due to sex (with similar ages and premedication) appeared unimportant.

*Blood Pressure.*—The systolic blood pressure following premedication with avertin varied markedly even with the same dose, particularly as to the time at which the change from normal occurred. Occasionally the initial fall was not observed until after the administration of the general anesthetic had been begun, owing probably to individual variability as to the rate of absorption from the rectum. The median picture was one of depression, which varied in degree from 10 to 40 per cent (the latter rarely), with an average fall of 18 per cent. The systolic fall was proportional to the dose of avertin, as indicated by the extremes in the entire group, but differences in the degree of fall in groups of equal age may be insignificant with a dose ranging from 60 to 100 mg. per kilogram of body weight (chart 1). Patients in the age range of from 40 to 65 years, particularly the aged, showed the greatest degree of depression. Women showed a greater systolic fall than did men under similar conditions of age and medication.

The diastolic pressure showed a much better correlation with the dose of the hypnotic administered than did the systolic pressure. Depression was the rule, the degree of which was somewhat less than the systolic change with small to medium doses (50 to 70 mg. per kilogram), but closely approximated the systolic change with larger doses. The fall increased with the dose and, irrespective of the dose, increased with age (chart 2). The diastolic pressure was depressed to a greater degree in females than in males of the same age under similar medication.

*Nature of the Anesthesia (Charts 1 and 2).*—The induction or transition period between the premedication state and surgical anesthesia was short. From 80 to 85 per cent of the anesthetics were considered good and the remainder fair or poor. Poor anesthetics were more frequent with small doses of avertin (from 50 to 70 mg.) than with large ones (from 85 to 100 mg.) and, so far as the supplements were con-

cerned, were more frequent with ether than with nitrous oxide and oxygen or with nitrous oxide, oxygen and ether. No poor anesthetics were recorded in the group receiving local anesthetics. One disagreeable feature observed in the use of local anesthesia was that patients reacted by movements, and occasionally complained even when medicated with from 90 to 100 mg. of avertin per kilogram of body weight. The anesthesia was somewhat better and more regular with young patients (under 18 years) than with older subjects. Smaller quantities of the supplementary anesthetic were required after large doses than after small doses of avertin. Heavily premedicated patients were simply nearer the stage of basal narcosis. Anesthesia was somewhat less satisfactory in female than in male patients, independent of age or the dose of avertin administered.

#### OBSERVATIONS DURING AND FOLLOWING OPERATIONS

*Pulse Rate.*—During operation the pulse rate increased from 10 to 40 per cent above normal, as indicated by the symbol *O* in the charts (part *B*). The increase was grossly proportional to the dose of the hypnotic administered under constant conditions as to age and supplementary anesthetic. Exceptionally, quite wide variations occurred, but generally with minimal doses of avertin. The nature of the supplementary anesthetic administered bore some relation to the changes in the pulse rate; i. e., with the exception of the age group from 1½ to 17 years, the increase was least with ether anesthesia and maximal with local anesthesia. The changes were greatest in young patients and decreased progressively with increasing age. Smaller changes occurred in females than in males.

Postoperatively the pulse rate varied from the level established during the operation with both the dose of the hypnotic and the nature of the anesthetic supplement; i. e., the pulse tended to increase with small doses of avertin (50 to 75 mg.) and to fall after maximal doses (above 85 mg.). Ether, nitrous oxide, oxygen and ether or local supplements in the main either inhibited a further rise or depressed the postoperative pulse rate.

*Blood Pressure.*—During the operation the systolic pressure increased as a rule and partially or completely compensated for the fall which occurred preoperatively, so that with the exception of those receiving small doses of avertin and the aged ones the values were from 3 to 10 per cent below (exceptionally above) the normal values. The degree of recovery was greatest with young and least with aged patients. The depression of the vasomotor center was proportional to the dose of avertin administered. Postoperatively the median systolic pressures were from 4 to 25 per cent below the original normal values; normal levels were exceptional.

Diastolic pressures both during operation and postoperatively were extremely variable. The significance of the data is questionable, but the systolic and diastolic oscillations were grossly parallel.

*Respiration.*—The respiratory rate increased from 30 to 60 per cent during the course of the anesthesia. The changes were greatest with nitrous oxide and oxygen and least with an ether supplement. The volume became distinctly more shallow than normal and compensated partly for the change in rate. The respiratory depression was apparent, and although it was possible to maintain surgical anesthesia in the absence of cyanosis in the great majority of patients, the margin of safety was narrow and the responsiveness to carbon dioxide or rebreathing was distinctly diminished during the first thirty to forty-five minutes of anesthesia. These difficulties diminished as the operation progressed owing to the fact that the depressive effects of avertin were wearing off. Postoperatively the respiratory rates varied on either side of normal, but more frequently remained slightly above normal for from one to two hours. The minute volumes remained below normal for variable periods (duration of postoperative sleep), and occasionally cyanosis developed.

*Restlessness.*—Movements during the period of operation rarely occurred, but were noted occasionally even after medication with maximal doses of the hypnotic (100 mg. per kilogram) and morphine ( $\frac{1}{6}$  grain) supplemented with nitrous oxide and oxygen. Such reactions were most frequent after small doses of avertin, but were not unusual in the presence of local anesthesia, irrespective of the dose of avertin administered.

Postoperative restlessness was observed more frequently than would be expected from previous reports. The frequency of occurrence bore an inverse relation to the dose of avertin. The frequency was lower with local than with other supplements. At least part of the postoperative reactions were due to the general anesthetic. Ether exaggerated the reaction to avertin to the greatest degree and nitrous oxide and oxygen least. The frequency of occurrence, as well as the percentage of the entire group of patients medicated postoperatively either for pain, restlessness or both, is illustrated in the charts. The postanesthetic movements noted following medication with avertin, although as frequent as with pentobarbital sodium, were distinctly less troublesome, and the patients required less nursing attention.

*Postoperative Sleep.*—The interval between the conclusion of the operative procedures and return of consciousness bore little if any relation to the dose of avertin administered. In general, the duration was greatest with ether, less with nitrous oxide, oxygen and ether and least with ethylene and oxygen. No postoperative sleep was observed

in the group receiving local anesthesia. It appears, therefore, that the duration of the operation and the degree of depression due to the anesthetic per se are of greater significance in governing the time of postoperative depression than the medication with avertin. The depressive effects of avertin have probably largely worn off by the time the surgical procedures are completed. Patients within the age range of from 1 to 18 years were medicated with from 90 to 100 mg. (median, 100 mg.) of avertin per kilogram of body weight. On the basis of the total time of unconsciousness (operation and postoperative sleep) the immature patients appeared most tolerant to maximal doses of avertin. However, both aged and young patients were more deeply narcotized than were patients of intermediate ages. The quantities of the supplementary anesthetics required in the extremes of age were less than in the intermediate ages (the hypnotic dose and anesthetic being constant), and the operative procedures were of less severity and of shorter duration in the young age group. Young patients are probably not more tolerant to avertin than are other age groups; on the contrary, as suggested by experimental studies of toxicity (Barlow), both young and aged patients are more sensitive to avertin, as evidenced by the greater percentage of patients in these two age groups who required no supplementary anesthetic. However, the lower frequency of organic lesions and the greater recuperative capacity of young subjects as compared with other age groups may be of significance during the postoperative as well as later periods.

*Nausea and Vomiting.*—Nausea was observed postoperatively in approximately 20 per cent of the general surgical patients. No clearcut relation between the frequency of its occurrence and the dose of avertin is apparent from the data. There are, however, indications that nausea occurred more frequently with small than with large doses and was somewhat greater in the presence of ether than with other supplements. Following nitrous oxide and oxygen anesthesia, emesis occurred less frequently (age group below 19 years excepted) than nausea. The majority of patients nauseated following anesthesia with supplements other than nitrous oxide and oxygen also vomited. Nausea and emesis were more frequent in females than in males in the age extremes, irrespective of the dose of avertin or the nature of the supplementary anesthetic. No difference related to sex was apparent in the group from 18 to 39 years of age. The divergence of this single group may be accidental.

*Amnesia.*—Eighty-five per cent of patients medicated with avertin had complete amnesia for from two to six hours after operation. The remaining 15 per cent had amnesia of more than six hours' duration. The period of amnesia was directly proportional to the dose of avertin.

In rare instances, irrespective of age, patients who received small doses of avertin supplemented with local anesthetics talked rationally during the course of the operation, and one patient subjected to a laminectomy remembered the incision being made.

*Urinary Findings.*—The first specimens of urine taken postoperatively showed traces of albumin in a certain percentage of all types of cases. The frequency was lowest in the orthopedic group, which included immature patients predominantly, and highest in the gallbladder and thyroid groups. In other surgical groups the frequency was intermediate. The albuminuria in patients free from albumin preoperatively ranged from a faint trace to 4 +. Albuminuria was present in 39 per cent of the entire group studied in detail. Relatively few of the specimens from females were obtained by catheterization; however, 28.7 per cent of the specimens from males likewise showed albumin, so that the incidence remained high. The specimens taken forty-eight hours after operation were albumin-free as a rule, but occasionally traces persisted for five or more days. The frequency of albuminuria bore little relation to the nature of the anesthetic supplement used, and the condition was observed with approximately the same frequency after medication with from 50 to 60 mg. as with from 80 to 90 mg. of avertin. The frequency bore a definite relation to the type of surgical case: greatest in the gallbladder group, next most frequent in the thyroid group and slightly less frequent in the group operated on for hernia and that treated by plastic surgery. The frequency was significantly higher in patients more than 35 years of age.

Hyaline and occasionally granular casts were observed postoperatively in 7 per cent of the total number of specimens studied. More than 90 per cent of the specimens showing casts postoperatively had not shown casts preoperatively. The specimens taken from forty-eight to seventy-two hours after operation were as a rule free from casts, but occasionally these persisted for several days. Specimens obtained from a 3 year old patient, although normal preoperatively, contained both albumin and casts for from seven to nine days postoperatively. Casts were usually absent from the urine of orthopedic patients and those who had undergone operations on the brain or the breast, but the frequency bore little relation otherwise to the type of surgical case. The frequency was no greater with large than with small doses of avertin, but this lack of correlation was only apparent in that older patients were medicated with minimal doses of the hypnotic.

Red and white blood cells were occasionally reported in the urine postoperatively, but in 2 of 3 cases the preoperative conditions remained unchanged. So far as cells were concerned the specimens were considered as containing none.

Traces of sugar were observed postoperatively in a small proportion of specimens. In one case values of 10 mg. per hundred cubic centimeters were observed, and the glycosuria persisted for more than a week. With few exceptions, however, glycosuria following this anesthetic sequence was no more frequent or greater in degree than in the absence of avertin.

#### OBSERVATIONS ON SPECIAL SURGICAL GROUPS

*Nature of the Anesthesia.*—Thyroid: The optimal anesthetic sequence for operations on the thyroid appeared to be morphine ( $\frac{1}{6}$  grain), atropine ( $\frac{1}{150}$  grain) and avertin (from 80 to 90 mg. per kilogram), supplemented with nitrous oxide and oxygen. All anesthetics obtained with this sequence were good. With smaller doses of avertin (from 60 to 70 mg.) anesthetics were distinctly less satisfactory, irrespective of whether nitrous oxide and oxygen or nitrous oxide, oxygen and ether were administered, but aged patients responded somewhat better than younger patients.

Gallbladder: In the group which was operated on for disease of the gallbladder the anesthesia and the relaxation obtained following medication with morphine and avertin (from 80 to 90 mg.) and the administration of nitrous oxide oxygen and ether were distinctly better than with lower doses of the hypnotic. Aged patients received smaller doses of avertin (from 50 to 70 mg.), and nitrous oxide and oxygen as a supplement. A greater percentage of fair anesthetics was obtained with this sequence than with that including nitrous oxide, oxygen and ether.

Brain: The optimal anesthetic sequence in this group, as judged by the observations made, was avertin in doses of from 50 to 70 mg. per kilogram, supplemented with local anesthesia. The frequency of movements during the course of the anesthesia was considerable, however. Ether, although somewhat less satisfactory owing to the greater frequency with which side actions occurred, nevertheless was the anesthetic of choice, in that relaxation was maximal and anesthesia complete. Avertin in doses of from 75 to 100 mg. per kilogram produced a narcosis of such degree that in 2 of the 13 patients no supplementary anesthetic was required. With such maximal doses of the hypnotic, local anesthesia was least and nitrous oxide, oxygen and ether most satisfactory.

Gynecological: Ninety-seven per cent of the anesthetics following medication with morphine ( $\frac{1}{6}$  grain), atropine ( $\frac{1}{150}$  grain) and 80 mg. of avertin per kilogram were satisfactory in the presence of a nitrous oxide, oxygen and ether supplement. Poor anesthetics were

exceptional (3 per cent). A greater percentage of "fair" anesthetics was obtained after medication with smaller doses, and although the anesthesia obtained in the presence of larger doses of the hypnotic was generally excellent, a greater percentage of poor anesthetics was noted than with medium doses.

*Pulse Rate.*—The median change in pulse rate following premedication was unimportant. No change was noted in the gynecological group, irrespective of the dose of the hypnotic. With the remaining groups the data suggest that directional changes are inverse to the change in systolic pressure. The correlation is imperfect, however; i. e., the variability is within a range of plus or minus 10 per cent, and may be insignificant.

During the operation the pulse rates of the thyroid group increased from 10 to 25 per cent above the values on admittance (100 per cent). The degree of change was proportional to the hypnotic dose. Comparable changes occurred with other groups. The altered pulse rate was probably compensatory for the altered blood pressure, but the correlation with either systolic or diastolic pressure was imperfect. Postoperatively the pulse rate remained somewhat above normal.

*Blood Pressure.*—In the thyroid group the depression of the systolic pressure following medication was proportional to the dose of the hypnotic administered; i. e., a median decrease of 7.5 per cent occurred with doses of from 60 to 70 mg. per kilogram and a fall of 16 per cent with from 80 to 90 mg. The systolic change was significantly greater in patients more than 50 years of age than in younger subjects, even with minimal doses of avertin. The diastolic pressures grossly paralleled the systolic levels, but were more variable. The aged group proved the exception in that, although the systolic pressure was reduced maximally, the diastolic pressure remained unchanged; i. e., it actually increased in relation to the systolic level. During the course of operation the systolic pressure increased above normal. The degree of rise from the preoperative level was greatest in the presence of small doses of the hypnotic. Postoperatively the systolic pressure decreased from the anesthetic level; i. e., with minimal doses of the hypnotic the pressures noted with middle-aged subjects remained slightly above normal, but fell below normal with maximal doses. The fall noted in aged patients was distinctly greater even with minimal doses of the hypnotic than the fall observed in younger subjects. The diastolic pressures remained within a normal range postoperatively.

In the gallbladder, brain and gynecological groups the median preoperative blood pressures differed insignificantly from those discussed for the thyroid group, but the rise during anesthesia as well as the postoperative fall was of smaller magnitude in these groups than in the thyroid group.



The rise in blood pressure during anesthesia was least with ether and greatest with nitrous oxide and oxygen. The supposedly transient fall in blood pressure as indicated by the preoperative level is probably of greater duration than is generally appreciated. The depression of the circulatory system by avertin is maximal during the thirty to forty minutes following rectal instillation, but persists to a modified degree for at least from ninety to one hundred and twenty minutes longer. The rise from the medication level which occurs on the administration of the general anesthetic is partly due to anoxemia per se, in that the rise is maximal with nitrous oxide and oxygen and minimal with ether. Surgical manipulation is likewise contributory, as indicated by the changes noted in the group receiving a local anesthetic (with cerebral involvement), as well as in the absence of any supplementary anesthetic. The postoperative fall is due partly to removal of the stimulant effects of the anesthetic and to surgical insult, but quite probably the persistent depressant effects of avertin are also contributory.

*Period of Postoperative Sleep.*—The duration of the postoperative unconsciousness was slightly longer in the thyroid, gallbladder and gynecological groups than in the massed series of surgical cases, irrespective of the dose of avertin administered or the nature of the anesthetic supplement used. Of the special surgical groups, those in the thyroid group recovered earliest, then those in the gallbladder and gynecological groups. In the brain group, no postoperative sleep was observed. The absence of significant postoperative depression in patients subjected to avertin and local anesthesia suggests that any effects of avertin persisting on conclusion of surgical procedures were insufficient to produce even moderate hypnosis, and that variations in the time required for the return of consciousness are explainable partly by the hangover effects of the supplementary anesthetic but more probably by the depressant effects of the surgical procedures. This explanation would seem to be substantiated by the fact that 2 patients who received large doses of avertin but no supplementary anesthetic, and who were subjected to operations on the brain slept one and seven and one-half hours, respectively.

*Restlessness.*—More than half the patients in the gallbladder, thyroid and gynecological groups were restless postoperatively. The frequency was in the order named. Patients in the thyroid group receiving medication with small or large doses of avertin were equally restless whether nitrous oxide and oxygen or nitrous oxide, oxygen and ether were used for supplementary anesthesia. Aged patients were more restless than younger subjects. In the gallbladder group patients were slightly more restless after small than after large doses of avertin, but those receiving large doses were given nitrous oxide, oxygen and ether while those receiving small doses (including a greater percentage of aged patients) received nitrous oxide and oxygen. The frequency with which restless-

ness occurred in the gynecological group was independent of the dose of avertin. The occurrence of restlessness in the brain group may have some relation to the dose of avertin administered, in that movements were less frequent after large doses than after small, independent of the supplementary anesthetic used. However, restlessness was much less frequent or entirely absent in the presence of local anesthesia, so the nature of the supplement contributes significantly to this unsatisfactory post-operative reaction.

From 50 to 100 per cent of all restless patients (with the exception of those in the brain group) received medication (indicated in the charts by a plus symbol) postoperatively.

*Nausea and Emesis.*—A small percentage of patients in each of the special surgical groups showed this reaction postoperatively. The fre-

TABLE 2.—Data in Relation to the Anesthetic Sequences

Anesthetic Sequence	Number of Cases	Number of Patients Showing Pulmonary Complications	Number of Complications per Cent of Total
Pentobarbital sodium, morphine and nitrous oxide and oxygen, nitrous oxide, oxygen and ether, or ether.....	378	1	0.264
Avertin, morphine and nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether .....	317	6	1.89
Morphine, atropine, nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether* .....	505	11	2.18
Morphine, atropine and ether.....	185	5	2.7
Local, with and without morphine.....	241	3	0.83

\* This group included the majority of poor anesthetic risks.

quency was greatest in the gallbladder group and next greatest in the gynecological group. The major portion of the nauseated patients also vomited, but occasionally emesis occurred in the absence of nausea.

#### UNTOWARD REACTIONS IN THE ENTIRE GROUP

One patient became hysterical and another vomited shortly after the administration of avertin. Postoperatively several patients complained of headaches, 1 suffered from a nervous chill, 1 became irrationally talkative and 4 (0.94 per cent of the group studied in detail) showed marked respiratory depression. Two of those showing respiratory depression received morphine postoperatively.

The blood pressure fell to moderate shock levels (90 mm. of mercury or less) at some time during the course of anesthesia or on conclusion of the operative procedures in approximately 10 per cent of the total series, and became imperceptible in slightly less than half the patients showing such reactions. Low blood pressure observed pre-operatively, i. e., after medication with avertin, as a rule returned to

normal or even above normal on administration of the general anesthetic, especially of nitrous oxide and oxygen. One half of the patients in whom shock reactions occurred were treated, usually with ephedrine ( $\frac{3}{4}$  grain [48.5 mg.]).

The frequency with which pulmonary complications ranging from definite bronchitis to atelectasis or pneumonia occurred during 1932 in a carefully studied group of general surgical cases with a series of anesthetic procedures is indicated in table 2.

Five deaths occurred in the group of 585 patients subjected to anesthetic and surgical procedures whose records were examined. One patient died one hour and a half after the removal of the major portion of one frontal lobe of the brain. The surgical procedures following which the other patients died were: an exploratory laparotomy; amputation of a leg; a gastric resection and the removal of an embolus. With the exception of the case in which a cerebral operation was performed, death occurred from ten hours to four days postoperatively. Avertin was not considered contributory to the fatal termination in any of the patients receiving the drug.

#### SUMMARY AND CONCLUSIONS

A general survey has been made of 1,831 records of anesthetics in which the patients were given morphine, atropine and avertin in doses of from 50 to 100 mg. (median 80 mg.) per kilogram of body weight, supplemented with several types of general anesthetics. The dose of the hypnotic was adapted to the age and general condition of the patient. Young patients (from 1 to 18 years) received maximal doses (90 to 100 mg. per kilogram). Aged patients as a rule received minimal doses. The optimal average adult dose of avertin appeared to be from 80 to 85 mg. per kilogram.

Ninety-two per cent of patients given premedication came to the operating room asleep. Occasionally (following medication with small doses as a rule) movements persisted. On arrival the patients were usually relaxed and, although satisfactorily analgesic, still responded to painful stimuli. The pulse rate was variable, and occasionally wide oscillations on either side of the normal rate were noted. The median rate increased slightly with small doses, but was either unchanged or slightly depressed by maximal doses. The extremes of age were associated with the least stability. The values of the blood pressure and pulse rate bore an inverse relation. The median blood pressure decreased 18 per cent, with a maximal range of from 5 above to 40 per cent below normal. Changes were minimal with the young and maximal with the aged patients. The respiratory rate was either unchanged or accelerated by medication; i. e., if a significant depression of respiration occurred the rate increased. The volume was rendered more shallow. The

minute volume was depressed in proportion to the dose of the hypnotic administered, and the percentile decrease varied from 22 per cent (with 70 mg. of avertin) to 40 per cent with maximal doses of the hypnotic. In exceptional cases, doses of 90 mg. reduced the minute volume more than 50 per cent.

Induction of anesthesia was rapid. From 80 to 85 per cent of the anesthetics were good; the remainder, fair or poor. Poor anesthetics were noted more frequently after small doses of avertin, and were more frequently observed with an ether supplement than with other general anesthetics. Movements occurred not infrequently in the course of local anesthesia following medication with avertin in doses as high as 90 to 100 mg. per kilogram. Patients in the thyroid, brain or gynecological groups responded less satisfactorily than did patients subjected to other types of operations. Young patients reacted better than aged ones and males somewhat better than females.

The pulse rate was accelerated from 10 to 40 per cent above the normal during anesthesia. The degree of change was variable, but grossly proportional to the dose of the hypnotic administered under constant conditions as to age and supplementary anesthetic.

The blood pressure increased during the course of operation and partially or completely compensated for the fall that occurred following premedication. The increase noted was greatest after minimal doses of avertin, and was of distinctly smaller magnitude in aged as compared with younger patients similarly medicated. The blood pressure of the thyroid group increased to a significantly greater degree than was observed in other surgical groups. The increase in diastolic pressure was usually of greater magnitude than the accompanying systolic change.

The respiratory rate increased from 30 to 60 per cent during anesthesia. The volume remained more shallow than normal. The respiratory depression apparent following premedication was partly counteracted by the anesthetic procedures. The margin of safety was narrowed, and the responsiveness to carbon dioxide was reduced. This disturbance diminished somewhat as the effects of avertin wore off. Postoperatively the respiratory rate remained slightly above normal for from one to two hours. The minute volume became either normal or approached the level at premedication. Exceptionally cyanosis developed.

Postoperative restlessness was observed in from 20 to 60 per cent of the patients, but was not troublesome from a nursing standpoint, although from 50 to 100 per cent of the restless patients received medication. The frequency with which restlessness occurred bore an inverse relation to the hypnotic dose administered. The complication was less frequent in aged than in younger persons. Little difference in this

respect was noted among the various surgical groups. At least part of the postoperative movements were due to the nature of the general anesthetic used, in that ether appeared to exaggerate the reaction, whereas movements were minimal in the presence of local anesthesia.

The duration of postoperative sleep bore little relation to the dose of avertin administered. The period of postoperative unconsciousness was significantly influenced by the nature of the anesthetic supplement and the duration and severity of the operative procedures. The duration was greatest with an ether supplement, and no sleep occurred after local anesthesia. The young and the aged patients appeared to be somewhat more sensitive to avertin than the normal adults.

Nausea and emesis occurred in approximately 20 per cent of the general surgical patients during the postoperative period. The frequency was greatest in the gallbladder group. The correlation of frequency was not close, but nausea and emesis appeared to be greater in females than in males and somewhat greater with small doses than with maximal doses of the hypnotic.

A moderate degree of renal damage occurred following the administration of avertin. Albumin (30 per cent frequency) and casts (7 per cent frequency) were observed in the specimens of urine taken twenty-four hours postoperatively. The majority of the specimens taken from forty-eight to seventy-two hours postoperatively showed no albumin or casts; exceptionally, traces persisted for several days. Traces of sugar were noted not infrequently, but were considered unimportant. However, 1 patient showed severe glycosuria postoperatively, and the condition continued for more than ten days.

Undesirable reactions following medication with morphine, atropine and avertin included a rather significant fall in the blood pressure and a definite depression of the respiratory volume, which occasionally was marked. If the depression was significant the rate became accelerated. The depression of respiration was apparent during the anesthesia in that the anesthetic margin was reduced. One patient became hysterical and another vomited shortly after the administration of the hypnotic.

Shock reactions of greater or less degree were observed in approximately 10 per cent of the patients either during the operation or during the postoperative period. The blood pressure became imperceptible in half of these and the patients required treatment.

The use of a morphine-atropine-avertin-supplementary anesthetic sequence reduced the frequency of pulmonary complications significantly as compared with a morphine-ether sequence. The frequency of pulmonary complications following the avertin sequence did not differ to a noticeable degree from that following a morphine-atropine-nitrous oxide, oxygen and ether sequence, especially when the greater number of poor operative risks in the latter group are taken into consideration.

The optimal anesthetic sequence, as judged by the infrequency with which undesirable side actions occurred and the significantly lower frequency with which pulmonary complications were observed as compared with any other anesthetic sequence tested, appears to be as follows: medication with pentobarbital sodium, morphine and atropine and the establishment of surgical anesthesia by means of a nitrous oxide, oxygen and ether supplement.

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# ACUTE INTESTINAL OBSTRUCTION

IMMEDIATE AND LATE RESULTS IN A HUNDRED CONSECUTIVE CASES

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This article is based on an analysis of the immediate and late results in one hundred consecutive cases of acute intestinal obstruction in which operation was performed at the Reading Hospital from August 1925 to August 1933.

Intestinal obstruction or ileus is the term used to indicate a stoppage of the fecal current, this condition being secondary to some pathologic process within or without the intestine, which is the primary condition. If the primary condition is mechanical, there is a mechanical obstruction; if it is due to a nervous or toxic influence which paralyzes the intestines, it is a paralytic or adynamic ileus, and if it is due to a spasm or contraction of the intestinal wall, it is dynamic ileus.

By far the larger number of instances of obstruction are due to mechanical agents. In the present series the causative factor was mechanical obstruction, and in all the cases the obstruction was acute and complete. Cases of pyloric obstruction, carcinoma of the rectum, postoperative ileus and mesenteric thrombosis were not included.

The data covering the end-results were obtained by a questionnaire sent the patient, and the information was received from the patient, a member of the immediate family or the family physician. The questionnaire was sent one month after the last patient was discharged from the hospital.

## CLINICAL DIAGNOSIS

The diagnosis is made largely on the basis of the history and the physical examination. Early diagnosis is not always easy. Usually, however, within a few hours, highly suggestive symptoms are present. Among these may be mentioned intermittent pains, nausea, vomiting, inability to pass gas, violent peristalsis and a failure of enemas to relieve the distress. The tighter the constriction is, the more sudden the attack. The pain usually becomes generalized, violent and continuous, with sharp exacerbations. The continuous pain is due to the constriction, the exacerbations to the colic of peristalsis as the intestine above the obstruction vainly lashes itself in its efforts to force material through the block. All the patients in this series had pain. Vomiting comes

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From the Surgical Service of the Reading Hospital.

Read before the Berks County Medical Society, Nov. 14, 1933.

on soon after pain. At first, it is reflex. It is accompanied by nausea and soon by severe retching, which continues practically without relief, whether food is taken or not. Depending on the size of the block, the material vomited consists of, first, gastric contents, next, bilious matter, then, brown intestinal contents and, finally, material which is fecal in character. In the present series eighty-four patients vomited; in nine the symptom was not mentioned in the history, and in seven there was no vomiting. A prominent symptom of intestinal obstruction is the complete cessation of the passage of gas and feces. It is important to remember, however, that in the inception there may have been a passage of flatus, or even a bowel movement, owing to peristalsis emptying the intestine below the site of the obstruction. As time goes on, in

TABLE 1.—*Causes of Intestinal Obstruction*

Pathologic Process	Number of Cases	Number of Deaths	Mortality, per Cent
Hernia.....	49	16	32.6
Adhesions.....	19	7	36.8
Carcinoma of the Intestine.....	13	8	61.54
Volvulus.....	5	2	40.0
Intussusception.....	4	3	75.0
Atresia of the Intestine.....	2	2	100.0
Gallstones.....	2	1	50.0
Concretions.....	2	2	100.0
Metastatic growths.....	2	0	0.0
Meckel's diverticulum.....	1	0	0.0
Tuberculous peritonitis.....	1	0	0.0

spite of the great desire on the part of the patient for an evacuation, there is complete failure. Enemas are returned clear or require siphoning off.

A serious evil in the management of all acute abdominal disorders is the administration of morphine before the diagnosis has been made. The warning of intermittent colicky pain is silenced, the medication alters the symptoms and produces new symptoms and, worst of all, much valuable time is lost.

Other symptoms of the condition are a progressively anxious expression, pallor, rapid and weak pulse, diminished output of urine, which contains large amounts of indican, subnormal temperature, dry tongue and foul breath, tympanitis and collapse.

#### LABORATORY DIAGNOSIS

There is not much material available for laboratory diagnosis, nor is there time for it. Naturally, a routine urinalysis is imperative, and a blood count should also be done. Leukocytosis is absent in the early stage. Later, incident to the dehydration brought about by vomiting,



a high leukocyte count may be present, with similar increases in the hemoglobin and red blood cells.

Blood chemistry is only of prognostic and therapeutic value. Elevation of the blood urea, decrease in the plasma chloride and alkalosis occur regularly in high obstruction after about two days of vomiting, but are not early signs of acute intestinal obstruction. In low obstructions these changes are usually absent.

Roentgen examination following the administration of barium sulphate by mouth should never be done in these cases, for it aggravates the condition, and the diagnosis can be made without it. Recently, the "flat plate" of the abdomen has been employed. This was used originally by Schwartz,<sup>1</sup> in 1911. Case<sup>2</sup> introduced the procedure in this country about the same time. In many hospitals the procedure is a routine in all cases in which intestinal obstruction is suspected. The patient is given an enema, and the picture is taken with the patient

TABLE 2.—*Age Incidence in the Hundred Cases Reported*

Age	Number of Cases
Birth to 5 years.....	9
6 to 10 years.....	1
11 to 20 years.....	1
21 to 30 years.....	9
31 to 40 years.....	6
41 to 50 years.....	19
51 to 60 years.....	21
61 to 70 years.....	21
71 to 80 years.....	8
81 to 90 years.....	5

standing up or lying down, depending on his condition. Normally, there is not enough gas in the small intestine to be recognized in a roentgenogram. In obstruction of the small intestine, collections of gas can often be seen early. There are two types of intestinal outline: (1) a herring-bone appearance, due to the gas giving a feathery or slashed appearance to the intestinal loop, and (2) a ladder arrangement of the shadows of the intestinal coils, when the distended loops lie parallel. The latter appearance is pathognomonic of acute obstruction requiring immediate surgical intervention. The herring-bone aspect signifies a degree of hindrance which constitutes a serious menace to the patient, but which has, in some instances, been seen to appear and later disappear under nonsurgical treatment.

If an obstruction of the colon is suspected, a barium enema should be given to prove and to locate it.

In table 2 the age incidence in the cases in this series is shown.

1. Schwartz, G.: Die Erkennung der tieferen Dünndarmstenose mittels des Röntgenverfahrens, Wien. klin. Wchnschr. 24:1386, 1911.

2. Case, James T.: Roentgenological Aid in the Diagnosis of Ileus, Am. J. Roentgenol. 19:413 (May) 1928.

The ages from 21 to 70 years present the greatest incidence, the average age being 48.7 years. The youngest patient was 2 days old, and the oldest 85 years. There were fifty-three females and forty-seven males.

The hospital incidence was in a ratio of one to four hundred and three admissions.

#### DIFFERENTIAL DIAGNOSIS

The lesion for which early simple intestinal obstruction is probably most often mistaken is the "simple belly-ache," under which category one might list indiscretions in eating, abdominal allergic reactions and acute enterocolitis. In these, however, diarrhea is usually a prompt symptom, and vomiting is much less in the foreground than in obstruction. Even while the early vomiting of intestinal obstruction is reflex, as it is in gallstone or renal colic, the vomiting of obstruction is more frequent, more urgent and more copious than in other types of reflex vomiting.

Simple obstruction of the intestine causes colicky pain and colics, but these are often unaccompanied by local signs, in contradistinction to all the other colics of the abdomen, which are soon followed by local tenderness over the seat of the lesion. The pain of intestinal colic quickly reaches its acme, and falls rather abruptly, being sustained for only two or three minutes and recurring again after a free interval. The duration of the painful seizures attending distress in the gall-bladder or kidney is much longer sustained.

Extra-abdominal lesions, such as syphilis of the central nervous system, tumors of the spinal cord, arthritis and tuberculosis of the spine, may cause rigidity of the abdominal muscles, but tenderness is usually absent. In the extra-abdominal lesions the pain is usually more continuous, and nausea and vomiting are not prominent. In the colics of gastric crises, other neurologic findings serve to identify the disease.

In strangulation obstruction a large number of conditions must necessarily be thought of in the differential diagnosis, including: all the abdominal colics, such as gallbladder and renal seizures; the inflammatory conditions, such as appendicitis, salpingitis, peritonitis and renal infections; pancreatic necrosis and diaphragmatic pleurisy, purpura and other cutaneous lesions, with hemorrhage into the intestinal wall, and torsion of other organs, especially cystic ovaries and even the testes. In the case of an ovarian cyst twisted on its pedicle, the stethoscope and the local examination serve to differentiate, and vomiting is usually less marked and even absent.

In many cases there is difficulty in arriving at an absolute definite diagnosis.

There is, however, one comforting fact, namely, that practically all the conditions with which acute intestinal obstruction is likely to be confused demand operation almost as imperatively as does intestinal obstruction.

When one waits until all the points in the differential diagnosis can be explained accurately the patient usually dies.

Twenty-five patients had abdominal operations previous to obstruction, but in five of these there was no logical causal relationship for the later diagnosis.

#### PROGNOSIS

In complete intestinal obstruction death is inevitable unless there is surgical intervention, and the longer surgical intervention is delayed,

TABLE 3.—*Previous Operation in Patients with Intestinal Obstruction*

Operation	Number of Cases
Appendectomy (approximately one half drainage cases).....	14
Laparotomy for trauma.....	2
Panhysterectomy for a malignant process.....	1
Cholecystectomy .....	2
Inguinal hernia .....	2
Exploratory laparotomy and appendectomy.....	1
Bilateral salpingectomy and appendectomy.....	1
Ovarian cyst and appendectomy.....	1

the smaller will be the patient's chance of recovery. Miller<sup>3</sup> stated that the mortality increases approximately 1 per cent with each hour of procrastination, and Moynihan said that any mortality over 10 per cent should be regarded as the "mortality of delay."

#### LEVEL OF OBSTRUCTION

It is generally recognized that obstructions of the colon are less fulminating than those of the small intestine. Furthermore, it is also true that obstructions high in the small intestine are more rapidly fatal than those situated lower. Of course, if interference with the mesenteric circulation is present, death will occur as quickly in one situation as in another, as a result of the infarction of the intestine. In the present series the small intestine was the site of the obstruction in seventy-seven instances, the large intestine in twenty-one cases and both in two instances.

3. Miller, C. Jeff.: A Study of Three Hundred and Forty-Three Surgical Cases of Intestinal Obstruction, *Ann. Surg.* 89:91, 1929.

## CAUSE OF DEATH IN ACUTE INTESTINAL OBSTRUCTION

Much experimental work has been done to show the exact cause of death in acute intestinal obstruction, and numerous theories have been advanced. In general the conclusions fall into three groups:

1. Invasion of the body by bacteria from the damaged intestine. This obstruction is often accompanied by peritonitis and organisms in the blood. However, death often occurs without peritonitis, and cultures from the blood, liver, spleen and other organs are sterile.

2. The nervous reflex theory has been advanced as the cause of death. Thus, in volvulus, especially of a large portion of the intestine, reflex shock seems to play a great part. Whenever the blood supply to the intestine is interfered with, the symptoms are fulminating and there are early necrosis and perforation.

3. Most investigators now agree that the symptoms of obstruction are due to the absorption into the system of poisonous material from

TABLE 4.—Mortality In Relation To Anesthesia

Type of Anesthesia	Number of Cases	Number of Deaths	Mortality, per Cent
Local (procaine hydrochloride).....	11	5	45.5
Nitrous oxide and ether.....	22	9	40.9
Nitrous oxide.....	10	5	50.0
Spinal.....	15	6	40.0
Ether.....	10	5	50.0
Spinal and general.....	18	11	61.1
Local and general.....	4	4	100.0

the obstructed intestine. This is the chemical poison or toxic theory. The possible routes by which the toxin enters the circulation are through the peritoneal cavity via the lymphatic stream or directly into the portal blood. There is some question as to whether the toxin is found in the lumen or in the mucosal cells. It has been shown experimentally by Scholefield<sup>4</sup> that bacteria and a highly organized mucosa are necessary factors. Furthermore, intra-intestinal pressure and time are important elements in the production of this toxin. Whipple<sup>5</sup> and Stone isolated, by precipitation with a solution of 95 per cent alcohol, a substance which resembled proteose. This could be redissolved in water, and was precipitated by half saturation with ammonium sulphate. One hundred milligrams of the substance was sufficient to kill a dog weighing 15 pounds (6.8 Kg.).

Sir Frederick Treves pointed out in his book on intestinal obstruction that the final outcome in these cases was not primarily dependent on the actual stoppage of the flow of material along the intestinal tract,

4. Scholefield, Bernard G.: *Guy's Hosp. Rep.* 77:160 (April) 1927.

5. Whipple, A. O.: *Safety Factors in the Treatment of Acute Intestinal Obstruction*, Boston M. & S. J. 197:218, 1927.

but rather on the absorption of toxic products from the disordered intestine, resulting in septic infection of the whole body. He stated that the subjects of acute intestinal obstruction die for the most part with the phenomena of septic poisoning, and if a certain stage has been passed, the mere relief of the obstruction does not save life.

Table 4 suggests that a simple type of anesthesia, such as local, nitrous oxide or spinal anesthesia, is less hazardous than a combination of any one of these with ether anesthesia.

#### TREATMENT

The essence of the treatment of acute intestinal obstruction is early diagnosis and early surgical intervention. When the decision to operate has been made, no time should be lost in preoperative preparation. During the time that preparations are being made in the operating room, the patient's stomach should be evacuated by lavage, and dextrose and physiologic solution of sodium chloride should be given intravenously and subcutaneously to restore the fluid balance and replace the lost chlorides.

When there is early surgical intervention, the choice of anesthetic is not so important; however, to administer inhalation anesthesia to a patient who has regurgitant vomiting and considerable distention, even though the stomach has been emptied, adds hazard to the operation. Spinal anesthesia is ideal.

The surgical procedure is based on its relation, not only to the pathologic condition present, but also to the condition of the patient. No more should be done than the patient's condition warrants. It is here that surgical judgment and experience count a great deal. In some instances, a complete operation may be performed, that is, finding and releasing the obstruction and restoring the continuity of the intestine, whether this is done by mere release of the constricted intestine or by resection.

In other cases, drainage of the intestine by enterostomy, exteriorization, cecostomy and colostomy is all that may be done with safety. In the latter cases, a secondary operation is often performed later.

The postoperative treatment is as important as the diagnosis and the operation, and varies in each instance. Three things are of paramount importance: The stomach must be emptied by lavage if necessary. Lost body fluids must be replenished in the form of hypertonic saline and dextrose solution. The patient's general condition must be guarded, with particular attention to the cardiovascular system.

#### RESULTS OF OPERATION

*Immediate.*—In my series fifty-nine patients survived and forty-one died. Of the forty-one who died, all had preoperative vomiting except

four. The four who did not have preoperative vomiting had a strangulated intestine at the time of the operation, and two required intestinal resections. There were twenty-five postmortem examinations. In most of the twenty-five, a continuation of the findings at operation was found, namely, peritonitis and gangrene of the intestine. In four cases there was massive postoperative pneumonia, in three, marked postoperative adynamic ileus, and one patient died on the operating table fifteen minutes after nitrous oxide anesthesia was started. The last mentioned patient had been toxic, with a diagnosis of strangulated inguinal hernia.

TABLE 5.—*Mortality In Relation To Operative Procedure*

Procedure	Number of Cases	Mortality
Repair of hernias.....	45	14
Release of adhesions.....	17	5
Reduction of volvulus and intussusception.....	5	1
Resection.....	9	6
Resection and drainage of the intestine.....	9	6
Enterotomy.....	4	3
Enterostomy.....	1	1
Cecostomy.....	4	3
Colostomy.....	4	1
Obstruction not found.....	1	1

TABLE 6.—*Comparative Mortality of Series of Various Authors\**

Series	Mortality, per Cent
Cornell: Ann. Surg. 95: 816, 1932.....	51.45
Deaver and Ross: Ann. Surg. 83: 571, 1926.....	42.0
Finney: Surg., Gynec. & Obst. 32: 402, 1921.....	26.0
Koslin: Ann. Surg. 95: 821, 1932.....	53.55
McFey: Arch. Surg. 25: 1036, 1932.....	31.0
Miller <sup>2</sup> .....	60.9
Rentschler.....	41.0
Seelaus: Pennsylvania M. J. 35: 17, 1931.....	53.0
Vidgoff: Ann. Surg. 95: 861, 1932.....	51.45

\* The statistics were not all based on the same premises.

and had vomited for four days prior to operation, having refused to permit surgical intervention. One died of a *Bacillus Welchii* infection.

Of the sixteen cases in which postmortem examination was not permitted, twelve died on the day of the operation. Four died following extensive intestinal resection; two others had gangrenous and necrotic intestines, but in neither case did the patient's condition warrant resection. Three patients who had intussusception had blood in the stool for more than forty-eight hours, and the abdomen was markedly distended prior to the operation; one refused to permit operation until it was practically too late and one died with the clinical diagnosis of bronchopneumonia seven days after the operation. Three patients were 80 years, or more, of age.

*Late.*—Forty-seven of those who survived stated that they are generally well; however, four have incisional hernias. Three had minor operations, irrespective of the original condition, and two had major operations, appendectomy and radical amputation of the breast for carcinoma. One woman had a hernia at the site of the operation, which was cured by operation, and at the end of two years had no complaint. Another also had an incisional hernia with intestinal obstruction which was cured by operation, but again a hernia resulted, which was repaired a second time; a year and a half after her third operation she was in excellent condition.

Two, who had a malignant process in the intestine, are still living; in one, fourteen months after a colostomy, the primary growth was inoperable, and the other was generally well and working one year after the excision of the intestinal growth. Several of the aged have afflictions such as myocardial degeneration.

Twelve are dead. Three died of a malignant process in the intestines. Two died as a result of intestinal obstruction caused by a metastatic malignant process. Two died of tuberculosis; one, of pulmonary tuberculosis six years after the operation for intestinal obstruction, and the other, two months after the operation of a continuation of tuberculous peritonitis. Another died following an operation for recurrence of the intestinal obstruction; both times the obstruction was due to adhesions. The four other deaths were a result of old age, one, a year, two, two years, and one, three years later.

#### CONCLUSIONS

1. The mortality following acute intestinal obstruction is too high.
2. The only way to reduce the mortality is to relieve the obstruction before it is too late.
3. Waiting for a perfect and detailed preoperative diagnosis is the cause of death in most of the fatal cases.
4. In a case of early obstruction, a complete operation can usually be safely performed. In late obstruction, one had better perform the operation in stages, rather than take too much chance on the life of the patient.
5. Death is due to three primary factors: obstruction of the fecal current, necrosis of the intestine and the production and absorption of toxins.

# SHOCK

## FURTHER STUDIES WITH PARTICULAR REFERENCE TO THE EFFECTS OF HEMORRHAGE

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In many of the experiments on shock which I have previously reported, sodium barbital was used as the anesthetic. Parsons and Phemister used ether or sodium barbital or either of these supplemented by morphine in most of their experiments. Similar findings were reported<sup>1</sup> by the two groups of investigators. Sodium barbital in the dosages employed in these experiments produces unconsciousness, an acceleration of the pulse rate, a decline in the pulse pressure, occasionally a drop in the arterial blood pressure, infrequently early death and frequently a moderate amount of capillary congestion and hemorrhage in some of the organs of the body. Most of these changes are produced by any agent which will produce profound anesthesia for a number of hours. It is unfortunate that the experimental production of a great many pathologic conditions has for humane reasons to be accompanied by a complicating factor such as an anesthetic. However, the finding that there was a loss of a sufficient part of the blood volume into the injured part to account for the low blood pressure in the experiments in which an extremity was traumatized, despite the fact that the anesthesia was profound, would seem to indicate that the circulatory systems of the animals were not necessarily markedly impaired by the anesthetic agents. In order to obtain further information, additional experiments were performed which are reported in the present paper.

The initial experiments consisted of studies of the alterations in the blood and various tissues of the body that are produced by profound anesthesia. This was followed by experiments in which shock was produced by traumatizing an extremity, several different anesthetics being used, and the local loss of fluid, as well as the changes in the

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This study was aided by a grant from the Fluid Research Fund of the Rockefeller Foundation.

1. Blalock, Alfred: Experimental Shock; the Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* 20:959 (June) 1930. Parsons, Eloise, and Phemister, D. B.: Haemorrhage and Shock in Traumatized Limbs, *Surg., Gynec. & Obst.* 51:196 (Aug.) 1930.



tissues, was studied. The effects of a low blood pressure produced by other means, as by injecting histamine and acetylcholine and by causing an increased intrapericardial pressure, were next determined. These experiments led to others in which the effects of maintaining the blood pressure at a low level by hemorrhage were studied. The results of the experiments on hemorrhage appear to be the most significant, and this paper deals primarily with them.

Probably the most generally accepted distinctive characteristics of shock and of hemorrhage are summarized in a recent editorial in *The Journal of the American Medical Association*,<sup>2</sup> as follows:

A recent paper<sup>3</sup> indicates that two criteria are available to distinguish between shock and hemorrhage: In shock the blood becomes more concentrated, as shown by specific gravity, hemoglobin and erythrocyte count; following hemorrhage, dilution of blood occurs. In shock there are widespread capillary dilatation of the viscera, congestion accompanied by edema, and petechial hemorrhages; following hemorrhage the tissues are anemic. The differentiation of hemorrhage and shock is of more than academic importance. It is well known that recovery follows the introduction of physiologic solution of sodium chloride into the circulation of patients suffering from the simple loss of blood. The futility of this procedure in shock has been proved beyond question. The increased permeability of the capillaries, which is a characteristic feature of shock, allows saline solution to escape rapidly into the tissues. Solutions containing acacia or dextrose have been found more effective than saline solutions but not so effective as the transfusion of blood. Even the latter is ineffective in profound shock.

The results obtained in the previous studies on traumatic shock by me and by Parsons and Phemister so clearly indicated that this condition could be attributed solely to the actual loss into the injured area of the various constituents of the blood that it seemed reasonable to believe that the same condition could be produced by hemorrhage alone.

#### GENERAL METHODS

Dogs were used in all of the experiments. They were maintained free of pain by the use of local or general anesthetics. A cannula that was connected to a mercury manometer was placed in the femoral or carotid artery for the determination of the blood pressure. Hematocrit determinations on venous blood were performed in duplicate by the use of Van Allen tubes. Immediately following the death of the animals, the abdominal and thoracic cavities were opened, and the organs were examined. The weights of the heart, lungs, liver, intestinal tract, exclusive of the stomach and esophagus, kidneys and spleen were determined. After removal of these organs without having ligated the blood supply, the quantity of free blood that remained in the pleural and peritoneal cavities was determined. Microscopic sections of tissues removed from the cardiac, pulmonary, hepatic, duodenal, renal, splenic, pancreatic, suprarenal and skeletal muscle were prepared and examined.

2. Shock, editorial, J. A. M. A. 100:46 (Jan. 7) 1933.

3. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. 14:360 (Sept.) 1932.

In the experiments in which an extremity was traumatized, the loss of fluid into the injured area was determined by a method that has previously been described.<sup>1</sup> In other experiments, histamine and acetylcholine were injected subcutaneously at frequent intervals in amounts sufficient to maintain the blood pressure at a low level. An increase in the intrapericardial pressure was produced by introducing fluid through a cannula that was anchored into an opening in the pericardium by the method employed by Cannon.<sup>4</sup> The blood pressure can be reduced to any desired level by this procedure. Most of the experiments in which the effects of hemorrhage were studied were performed without general narcosis. Pain was prevented by the injection of procaine hydrochloride at the sites where cannulas were introduced for the determination of the blood pressure and for the removal of blood. A few of the animals became restless during the course of the observations and were given small dosages of morphine. The results were the same in the experiments in which procaine hydrochloride alone was used as in those in which the procaine hydrochloride was supplemented by a small amount of morphine. The experiments in which the blood pressure was maintained at a low level as a result of hemorrhage may be divided into five groups. In the first group, blood was withdrawn slowly from the femoral artery until the systolic pressure was reduced to less than 70 mm. of mercury. When the pressure rose above this level, additional blood was removed. After a sustained decline in the arterial pressure to less than 70 mm. was produced, the animal was allowed to die without further removal of blood. The desired condition was to have the animal live with a low blood pressure as long as possible, and it required a great deal of care in the removal of blood in order to do this successfully. In the remaining four groups of experiments, the blood pressure was reduced to a low level by hemorrhage, and it was maintained fairly stationary at this low point by the further removal of blood, if the pressure rose, or by the introduction of blood, if the pressure fell. It is to be emphasized that large amounts of blood were usually not introduced at one time. An attempt was made to inject just enough to keep the pressure from falling to too low a level. In one group of experiments the blood that was removed from the animal and subsequently injected was prevented from clotting by defibrination; in another group it was mixed with sodium citrate, and in still another it was placed in a solution of heparin. In the fifth group of experiments, the blood was transfused by the direct method from a suitable donor.

#### OBSERVATIONS

*Normal Controls.*—The sudden death of seven normal animals was produced in order that the weights of the organs might be determined, and that normal tissues might be obtained for study. In some instances death was caused by electrocution and in others by opening the pleural cavity of animals anesthetized for a few minutes by ether. The average weights of the organs are given in the table, as are those obtained in the remaining groups of experiments. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled in terms of body weight 5.93 per cent.

*Effects of Sodium Barbitol Anesthesia.*—Six experiments were performed in which the effects of barbitol anesthesia were studied. The

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4. Cannon, W. B.: Traumatic Shock, in Surgical Monographs, New York, D. Appleton and Company, 1923, vol. 1, p. 63.

anesthetic was injected intravenously in the dosage of 0.3 Gm. per kilogram of body weight. The administration of barbital was followed by an increase in the pulse rate and a decrease in the pulse pressure. The average duration of the control experiments on the effects of barbital anesthesia alone was six hours and thirty-two minutes. The average mean arterial blood pressure before the injection of barbital was 133 mm., and at the completion of the experiments, 121 mm. In some instances the concentration of the red blood cells increased, and in others it diminished. Death of the animals was produced in some experiments by electrocution and in others by the opening of the pleural cavity.

### *Weights of Organs*

Experimental Condition	Number of Experiments	Average Weight of Dogs, Kg.	Weight of Organs in Grams per Kilogram of Body Weight							
			Right Lung	Left Lung	Heart	Liver	Spleen	Right Kidney	Left Kidney	Intestinal Tract
Control.....	7	11.2	5.43	3.81	7.80	29.48	1.86	2.49	2.66	41.26
Ether control.....	5	13.3	5.33	3.62	6.71	25.59	2.85	2.50	2.47	34.55
Barbital control.....	6	16.3	5.50	3.75	7.73	27.15	2.99	2.83	2.91	33.44
Ether and trauma.....	10	14.3	4.32	3.23	7.34	28.29	3.12	2.74	2.79	35.69
Barbital and trauma.....	12	13.8	5.29	3.90	7.44	29.76	2.84	2.76	2.85	36.57
Ether and hemorrhage....	9	12.1	4.83	3.43	7.31	29.69	3.17	2.56	2.62	36.80
Barbital and hemorrhage	8	13.5	4.64	3.20	7.69	27.24	2.96	2.41	2.47	31.59
Spinal anesthetic and trauma.....	5	14.3	5.21	3.80	7.48	31.73	3.54	2.82	2.80	38.26
Spinal anesthetic and hemorrhage.....	5	15.2	5.06	3.59	7.46	27.67	3.08	2.28	2.35	32.40
Ether and histamine.....	5	10.8	4.80	3.35	7.01	33.45	2.58	2.67	2.67	35.50
Barbital and histamine...	6	15.8	5.61	4.06	7.71	37.06	3.30	2.62	2.75	36.53
Hemorrhage; no replacement.....	7	13.9	4.48	3.44	7.03	27.26	3.33	2.54	2.64	33.26
Hemorrhage; replaced defibrinated blood.....	9	13.05	4.78	3.31	7.17	32.11	3.54	2.69	2.91	36.85
Hemorrhage; direct transfusion.....	4	9.2	5.04	3.88	8.13	33.29	3.65	2.85	2.91	37.56
Acetylcholine.....	2	10.06	4.62	3.31	5.99	29.78	3.63	2.63	2.74	40.93
Increased intrapericardial pressure.....	2	12.9	5.08	3.80	6.34	29.09	4.00	3.37	3.43	36.71

Autopsies revealed slight reddening with a small amount of blood in the lumen of the intestinal tract in four of the six experiments. The lungs presented a few hemorrhagic areas in five experiments, and the wall of the gallbladder was somewhat thickened in five. The most marked microscopic alterations in the tissues that were removed for study were: (1) There were moderate capillary congestion and slight hemorrhage in the suprarenal glands, with a great many polymorphonuclear leukocytes in the cortex surrounding the medulla; (2) the small intestinal tract showed slight congestion and hemorrhage; (3) there was slight congestion of the vessels of the heart; (4) the kidneys revealed moderate capillary congestion and dilatation, and (5) there were a moderate amount of congestion and dilatation of the pulmonary capillaries, and atelectasis. The average quantity of blood remaining in the pleural and peritoneal cavities following the removal of the organs equaled 5.2

per cent of the body weight or approximately half of the estimated total blood volume.

*Effects of Ether Anesthesia.*—Five experiments were performed in which the effects of ether anesthesia administered by inhalation were studied. The depth of anesthesia was such that the muscles were well relaxed. The eye reflexes were not abolished. Ether caused an increase in the pulse rate and a decrease in the pulse pressure. The average duration of the studies was six hours and twenty-two minutes. The average mean arterial blood pressure before the administration of ether was 138 mm., and at the completion of the observation period it was 105 mm. The concentration of the red blood cells increased in all of the experiments. The average hematocrit reading changed from 40.6 per cent during the control period to 49.9 per cent at the conclusion. Postmortem examinations showed scattered hemorrhages in the jejunum and ileum. The mucous membrane of the intestinal tract except at the site of the hemorrhage was essentially normal in color. The lungs presented one or more areas into which hemorrhage had occurred. The liver in some instances was dark. In one experiment there was a great deal of hemorrhage in the endocardium of the left ventricle. On microscopic examination, the following changes were observed: A moderate amount of congestion and hemorrhage were present in the suprarenal glands. A few of the cells of the medulla were undergoing necrosis. A moderate number of polymorphonuclear leukocytes were present in the cortex. The duodenum showed moderate capillary congestion and dilatation. There were slight capillary congestion and hemorrhage in the cardiac muscle in some experiments. The gallbladder was slightly edematous in a few instances, and there was capillary congestion. There were capillary congestion and dilatation in the kidneys. The liver showed vacuolation, a good deal of hemorrhage and congestion and a moderate number of polymorphonuclear leukocytes. The lung was partially atelectatic, and capillary dilatation and congestion were present. A moderate amount of congestion was present in the pancreas. The spleen showed focal necrosis of the lymphoid tissue. The average amount of blood remaining in the pleural and peritoneal cavities following the removal of the organs equaled 4.2 per cent of the body weight.

In summary, the alterations in the tissues that were produced by ether anesthesia were definitely more marked than those found in experiments in which sodium barbital was used as the anesthetic.

*Barbital and Hemorrhage.*—The animals were anesthetized by the usual amount of sodium barbital, and three hours later the removal of blood in small amounts at frequent intervals was begun. This was continued until death resulted. Eight such experiments were performed.

The average duration of the studies was five hours and forty-one minutes. The average amount of blood removed in terms of body weight equaled 4.21 per cent. The blood pressure did not remain at a low level for more than an hour in any of the experiments. The concentration of the red blood cells increased in five experiments and decreased in three. The average hematocrit readings at the beginning and end of the experiments were 46.8 and 49, respectively. The average amount of blood left in the pleural and peritoneal cavities after the removal of the organs equaled 1.34 per cent of the body weight. The changes in the tissues will not be described in detail. It suffices to state that they were slightly more marked than those found in the experiments in which the effects of barbital alone were studied. As has been stated, the blood pressure was at a low level for only a short while preceding the death of the animals.

*Barbital and Trauma.*—Twelve experiments were performed in which one of the posterior extremities was traumatized after the animals were anesthetized with barbital. The amount of barbital used was 0.3 Gm. per kilogram of body weight. The average time elapsing between the initiation of the trauma and death was five hours and twenty-eight minutes. The average difference in the weights of the traumatized and nontraumatized extremities in terms of body weight was 4.5 per cent or a little less than half of the estimated total blood volume. The average length of time that the blood pressure remained at a low level before death took place was approximately one and one-half hours. An increase in the concentration of the red blood cells occurred in nine experiments, and a decrease was found in the remaining three. The average amount of blood remaining in the cavities after the removal of the organs was 2 per cent of the original body weight. The gross and microscopic changes in the tissues were slightly but definitely more marked than those encountered in the experiments on the effects of barbital alone. Early necrosis of some of the cells of the suprarenal glands, duodenum, liver and spleen was observed. In several of the experiments there was a great deal of hemorrhage into the intestinal tract.

*Ether and Hemorrhage.*—Nine experiments were performed in which blood equaling 1 per cent of the body weight was removed at one hour intervals from dogs anesthetized by ether. This was continued until death resulted. The average duration of the experiments was three hours and forty-one minutes. The average loss of blood resulting in death in terms of body weight was 4 per cent or less than half of the total blood volume. The usual length of time that the blood pressure remained at a low level was slightly more than one hour. There was a decrease in the concentration of the red blood cells in six experiments

and a slight increase in the remaining three. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.7 per cent of the body weight. The gross and microscopic alterations in the tissues were not quite so marked as those found in the experiments in which the effects of ether alone were studied. It is to be remembered that the latter experiments were of longer duration. In several experiments there were a few small hemorrhagic areas in the intestinal tract.

*Ether and Trauma.*—Ten experiments were performed in which one of the posterior extremities of dogs anesthetized by ether was traumatized. The experiments were continued until death occurred. The average duration was five hours and ten minutes. The average difference in the weights of the injured and noninjured extremities in percentage of body weight was 4.46. The duration of the low blood pressure preceding death varied from thirty minutes to three hours. There was an increase in the concentration of the red blood cells in eight experiments and a dilution in the remaining two. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.7 per cent of the body weight. In several of the experiments there were many hemorrhagic areas with free blood in the intestinal tract. The suprarenal glands, liver and duodenum showed on section in some instances a moderate amount of hemorrhage and congestion and slight necrosis of the cells. On the whole, the alterations were slightly more marked than those encountered in the experiments in which the effects of ether alone were studied.

*Spinal Anesthesia and Hemorrhage.*—Spinal anesthesia was produced in this and in the subsequent group of experiments by the injection of 1 per cent procaine hydrochloride into the spinal canal in the lumbar region. A small amount of morphine was given subcutaneously previous to the injection of procaine hydrochloride. If a definite decline in the blood pressure followed the injection of the drug, the effects of hemorrhage or of trauma were not studied, since the tolerance to either of the procedures is markedly affected by a low blood pressure. One animal died one hour after 2 cc. of procaine hydrochloride had been injected into the spinal canal. No blood was removed, and no trauma was produced. It was observed at autopsy that the duodenum was markedly reddened and that the jejunum, ileum and large intestine were reddened to a lesser extent. The liver was dark. Rather marked alterations were found in the organs on microscopic study. The concentration of the red blood cells was increased.

Five experiments were performed in which the effects of spinal anesthesia and hemorrhage were studied. Blood equaling 1 per cent of the body weight was withdrawn at hourly intervals until death resulted.

The average duration of the experiments was four hours and thirteen minutes. The average amount of blood removed in terms of body weight was 4.8 per cent or approximately half of the total volume. The concentration of the red blood cells decreased in two experiments, remained the same in two and increased in one. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.25 per cent of the body weight. The mucous membrane of the intestinal tract was found to be very red in two of the experiments and slightly red in two others. Microscopic examination showed capillary congestion in most of the organs and hemorrhage in some.

*Spinal Anesthesia and Trauma.*—Five experiments were performed in which one of the posterior extremities was traumatized under spinal anesthesia. The average duration of the experiments was six hours and fifty minutes. The average difference in the weights of the traumatized and nontraumatized extremities equaled 4.45 per cent of the body weight. The blood pressure remained at a low level prior to death for varying periods. The red blood cells became more concentrated in all of the experiments. The average quantity of blood in the cavities after the removal of the organs equaled 1.53 per cent of the original body weight. The mucous membrane of the intestinal tract and the duodenum in particular was moderately red in all of the experiments. The microscopic alterations in the tissues were slightly more marked than those found in the experiments in which hemorrhage was carried out under spinal anesthesia. The changes were probably a little less marked than those found in the experiments in which trauma was produced in animals anesthetized by barbitol or ether.

*Barbital Anesthesia and the Injection of Histamine.*—Six experiments were performed in which histamine was injected subcutaneously into dogs anesthetized by barbital. The average duration of the experiments was five hours and twenty-six minutes. The blood pressure was maintained depressed below its normal level during this time, and it was kept at a low level for approximately two hours. The red blood cells became more concentrated in all of the experiments. The average quantity of blood remaining in the pleural and peritoneal cavities after removal of the organs was 3.56 per cent of the body weight. Reddening of the skin was observed in most of the experiments. The vessels of the intestinal tract became very prominent. At autopsy, the mucous membrane of the small intestines was found to be quite reddened, and in some instances free blood was present in the lumen. The microscopic alterations in the tissues were slightly more marked than those found in the experiments on the effects of barbital alone or ether alone. Certainly the difference was not great. The most evident difference was in the

liver, where it seemed that the administration of histamine resulted in greater changes.

*Ether and Histamine.*—Five experiments were performed in which the effects of the injection of histamine into animals anesthetized by ether were studied. The results were practically identical with those obtained in the experiments in which the dogs were anesthetized with barbital and in which histamine was injected.

The changes that are noted following the injection of histamine are not dependent on the associated anesthesia. This was demonstrated in one experiment in which only local anesthesia was used. The changes in the tissues were marked.

*Effects of the Injection of Acetylcholine.*—Two experiments were performed in which acetylcholine was injected intramuscularly into dogs narcotized by 0.033 Gm. of morphine. Sufficient acetylcholine was injected at frequent intervals to keep the mean arterial blood pressure at approximately 75 mm. for three hours. At the end of this time, the animals were killed. There was a marked increase in the concentration of the red blood cells. The blood remaining in the cavities after the removal of the organs equaled 3.46 per cent of the body weight. In both experiments reddening of the mucous membrane and hemorrhage into the intestinal tract were observed. In one of these the mucous membrane was beefy red in appearance. The liver showed a dark discoloration, and the wall of the gallbladder was thick and edematous. Microscopic study showed capillary congestion in all of the tissues studied except the skeletal muscle. There was hemorrhage into the liver and small intestines, and necrosis of some of the cells of the liver, duodenum and spleen.

*Effects of Increased Intrapericardial Pressure.*—Two experiments were performed in which the blood pressure was reduced by introducing fluid under pressure into the pericardial cavity. The animals were given a preliminary injection of morphine. Ether and artificial respiration were administered during the time that the cannula was being introduced into the pericardium. As soon as the chest was closed tightly, they were discontinued. The mean arterial blood pressure was maintained slightly below 70 mm. for three hours. At the completion of this time, the animals were killed. There was a marked increase in the concentration of the red blood cells. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 4.74 per cent of the body weight. Autopsy in one experiment showed marked reddening of the mucous membrane of the duodenum and the upper ileum; the gallbladder wall was thick and edematous, and there was hemorrhage in the endocardium. In the other experiment, the mucous membrane of the intestinal tract was beefy red,



and there was free blood in the lumen. The lungs and liver showed hemorrhagic areas, and the wall of the gallbladder was thick and edematous. The most marked changes on microscopic examination were observed in the duodenum and liver, where there were capillary congestion, hemorrhage and necrosis. The alterations in the suprarenal glands were surprisingly minor in degree.

*Effects of Hemorrhage Without Transfusion.*—Seven experiments were performed in which blood was removed in small amounts at frequent intervals until the mean arterial pressure was approximately 70 mm. If the blood pressure rose, additional blood was removed. The animal was allowed to die as a result of the removal of blood with the idea in mind of having the blood pressure remain at a low level as long as possible. No general anesthetic was used in these experiments, and pain was prevented by the injection of procaine hydrochloride at the sites where the cannulas were introduced into the blood vessels. The average duration of the experiments was six hours but the greater part of the time was consumed in producing a decline in the pressure from which recovery would not result. The interval elapsing between the time of the last removal of blood and of death averaged only one hour and twenty-six minutes. Although the blood pressure did not remain at a low level for an extended time, the mean arterial pressure and the pulse pressure were definitely lessened throughout the experiments. The average amount of blood removed in the different experiments equaled 4.3 per cent of the body weight. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.48 per cent of the body weight. There was a decrease in the concentration of the red blood cells in five experiments and an increase in two. In two experiments blood-stained material was passed from the rectum. In another, vomiting occurred two hours following the beginning of the experiment.

Autopsies were performed immediately following death. The mucous membrane of the intestinal tract was redder than normal in all of the experiments and blood-stained material was present in the lumen of the intestines in six of the seven experiments. The duodenum and jejunum presented the most marked alterations, but in some instances the ileum and large intestines showed reddening and hemorrhage also. Hemorrhagic areas were present in the lungs in some experiments. The following changes were observed on microscopic examination: The suprarenal glands showed fairly marked capillary congestion and hemorrhage and necrosis of some of the cells. Many polymorphonuclear leukocytes were located in the cortex surrounding the medulla. Slight vacuolation was present. The duodenum showed dilatation and thrombosis of capillaries, hemorrhage and necrosis of some of the mucous

membrane. There were slight hemorrhage and capillary congestion in the heart muscle. The skeletal muscle was essentially normal. Capillary congestion and dilatation were present in the kidneys. The liver showed capillary congestion, hemorrhage and necrosis of the liver cells. The location of the necrosis was variable. Atelectasis and capillary congestion were present in the lungs. There was a moderate amount of capillary congestion in the pancreas. The spleen showed hemorrhage into and some necrosis of the malpighian bodies.

*Effects of Hemorrhage and of Autotransfusion with Defibrinated Blood.*—Nine experiments were performed in which the blood pressure was reduced to a low level by hemorrhage and in which death was postponed by introducing blood when the blood pressure reached an extremely low level. The blood that was removed from the animals was defibrinated and strained through linen and kept at body temperature. Procaine hydrochloride was used at the sites where the cannulas were introduced. In four of the experiments, the animals were given 0.016 Gm. of morphine. No evidence of a reaction as a result of the introduction of blood was obtained in any of the experiments. The average amount of blood removed in the different experiments equaled 4.58 per cent of the body weight, and the average quantity replaced equaled 1.62 per cent of the body weight. In two of the experiments all of the blood that was removed was reintroduced, and yet the animals died. The average duration of the experiments was four hours and forty-four minutes. The blood pressure remained at a low level during the greater part of the duration of all of the experiments. These studies were of shorter duration than those reported in the previous group in which no blood was replaced, but the blood pressure remained at a low level for a longer time in the present experiments. There was an increase in the concentration of the red blood cells in four experiments and a decrease in five. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 2.28 per cent of the body weight.

The alterations in the tissues will not be described in detail. They were definitely more marked than those encountered in the last group of experiments in which blood was removed and none was replaced. This difference is probably due to the fact that the blood pressure remained at a low level for a longer time in the present studies, or possibly the defibrinated blood resulted in alterations.

*Effects of Hemorrhage and of Autotransfusion with Blood Collected in a Solution of Heparin.*—Three experiments were performed in which the blood that was removed was placed in a solution of heparin to prevent it from clotting. When the blood pressure reached a low level, the heparinized blood was injected intravenously. Two of the experi-

nents were unsatisfactory in that a severe reaction followed the introduction of the blood. The results in the remaining experiment were approximately the same as those obtained in the studies in which defibrinated blood was injected.

*Effects of Hemorrhage and of Autotransfusion with Blood Collected in a Solution of Sodium Citrate.*—Four experiments were performed in which the blood that was removed was collected in a 2.5 per cent solution of sodium citrate. This blood was injected intravenously when the blood pressure reached a low point. A fairly severe reaction was associated in two of the experiments with the giving of the blood, and these studies were discarded. The blood pressure remained at a low level for five hours in one of the remaining experiments and for seven hours in the other. All of the blood that was removed was replaced. There was a marked increase in the concentration of the red blood cells. The average amount of blood remaining in the pleural and peritoneal cavities after the removal of the organs was 2.58 per cent of the body weight. At autopsy, all of the mucous membrane of the intestinal tract was dark red, and there was a great deal of blood in the lumen. The liver was dark and contained much blood. The alterations in the tissues that were observed on microscopic study were marked.

*Effects of Hemorrhage and of Direct Transfusion.*—Four experiments were performed in which the blood pressure was maintained at a low level for a considerable time by the removal of blood and the introduction of blood by the direct method from a suitable donor. The recipient in all instances was a smaller dog than the donor. Hematocrit readings on the blood of the two animals were approximately the same. No evidence of a reaction as a result of the transfusion was obtained in these experiments. Pain was prevented by the local use of procaine hydrochloride. The average duration of the experiments was seven hours and thirty-four minutes. The blood pressure was lower than normal during the entire time. The average mean arterial pressure remained depressed below 75 mm. for three hours in three of the experiments and one hour in the other. The average time separating the last removal of blood and death was two hours and thirty-one minutes. During this time a good deal of blood was injected. The average quantity of blood that was removed in terms of body weight equaled 32 per cent, while the average quantity that was introduced equaled 46 per cent. It is to be observed that all of the animals died despite the fact that a slightly greater quantity of blood was injected than was removed. As has been stated, the blood pressure was reduced to a low level by hemorrhage before any blood was injected. There was an increase in the concentration of the red blood cells in all of the experiments. The average quantity of blood remaining in the pleural and

peritoneal cavities after the removal of the organs equaled 2.2 per cent of the body weight. The gross and microscopic alterations in the tissues were marked. The mucous membrane of the intestinal tract was red, and free blood was present in the lumen of the tract. Hemorrhagic areas in the lungs were noted in two animals. In one experiment the wall of the gallbladder was thick and edematous. On microscopic examination, the suprarenal glands showed vacuolation, hemorrhage, capillary congestion, an occasional cell with a necrotic nucleus and polymorphonuclear leukocytes in the cortex. The duodenum showed dilatation and thrombosis of the capillaries and complete necrosis of some of the crypts. Hemorrhage and capillary congestion were present in the heart muscle. The skeletal muscle was essentially normal. The liver showed hemorrhage, congestion and necrosis of liver cells. Capillary congestion and dilatation were noted in the kidneys and lungs. Focal necrosis of lymphoid tissue was present in the spleen. The pancreas showed a moderate amount of capillary congestion.

*Effects of Hemorrhage After Ligation of the Bile and Pancreatic Ducts.*—With the idea in mind that the bile and pancreatic juice might in the presence of a low blood pressure be responsible for the alterations in the mucous membrane of the intestinal tract, two experiments were performed in which the ducts were doubly ligated and divided. Five days later in one experiment and twelve days later in the other, the blood pressure was reduced to a low level and maintained there as long as possible by the gradual withdrawal of blood. In one experiment, the mucous membrane was slightly less red than that found in the experiments on hemorrhage alone. In the other experiment, the usual amount of reddening was observed. These experiments indicate that the bile and pancreatic juices are not responsible in the main for the changes that were observed. It is realized that there are other juices that pass into the intestinal tract which might exert an effect.

*Weights of the Organs in the Various Experiments.*—The weights of most of the organs of the body were determined in all of the experiments because it was believed that information as to the location of fluid that escaped from the blood stream could be obtained in this manner. All of the weights are expressed in grams per kilogram of body weight of the animal. The weights of the organs of a group of normal dogs were first determined. The death of most of the animals was produced by electrocution. This method produces a contraction of the spleen, and hence the weights of this organ are probably smaller than they should be. The organs were removed in the same manner in all experiments. The attachment of the organ, including the blood supply, was severed, and the blood that flowed out without pressure on the part was allowed to escape. The material that was present in the lumen

of the intestinal tract was removed before the weight of the tract was determined. There was a great variation in the weights of the individual organs as expressed in grams per kilogram of body weight in the different animals of the same group of experiments. This variation was greater than the difference in the average weights of the organs in the different groups of experiments. No attempt was made to obtain dogs of the same weight and state of bodily nutrition. The differences in the weights of the organs in the various groups of experiments were not great enough or sufficiently constant to allow any conclusions to be drawn as to the distribution of the loss of fluid. In fact, the average weights of the organs except for the intestinal tract and spleen in the control experiments were approximately the same as those obtained in the other studies. The liver was somewhat heavier in the experiments in which histamine was injected. The results of these determinations are given in the table.

#### COMMENT

Concerning the causes of traumatic shock, Cannon stated,<sup>5</sup> "One of the central problems, if not the most important central problem, of shock is that of discovering the reason for the lowered arterial pressure. The various theories which have been suggested to account for shock are all directed towards the solution of this problem." When hemorrhage occurs from a large blood vessel, a diminution in the circulating volume of blood results. Owing to vasoconstriction, the blood pressure may remain at its normal level. However, if the decrease in the blood volume is too great to be compensated for by vasoconstriction, the blood pressure falls. This mechanism of the production of shock as a result of uncomplicated hemorrhage seems to be generally accepted. On the other hand, there is a good deal of disagreement as to the cause for the decline in the blood pressure following injury to large masses of tissue. It is to be clearly understood that I do not refer to the decline in the blood pressure noted in primary shock or collapse in which the drop in pressure is rapid, is noted immediately following the injury or operative procedure and is usually of short duration. I refer to secondary shock in which the decline in blood pressure occurs usually an hour or more following the injury. A consideration of the various theories which have been offered in an effort to explain secondary shock will not be gone into here. Blalock<sup>1</sup> and Parsons and Phemister<sup>2</sup> showed that there was a loss of a sufficient part of the blood volume into the injured area following trauma to an extremity to account for the decline in blood pressure in animals anesthetized by sodium barbital or ether. It is shown in the present experiments that similar results are

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5. Cannon,<sup>4</sup> p. 15.

obtained when trauma is performed in animals in which anesthesia is produced by the injection of procaine hydrochloride into the spinal canal.

It is well known that there are frequently contributing factors, such as cold, insufficient fluids, anesthesia and operation, which further the development of shock. The manner in which ether anesthesia exerts at least part of its ill effects is demonstrated by the present experiments in which ether was administered for long periods. Capillary congestion and hemorrhage were noted in many of the organs. These alterations appeared despite the fact that the blood pressure did not decline greatly. If changes such as these appear in normal anesthetized animals, it is only natural to suppose that similar alterations which are associated with a low blood pressure as a result of uncomplicated hemorrhage or trauma will be accentuated by the administration of ether anesthesia.

As Cannon has stated, the central problem in the study of traumatic shock has to do with the reason for the lowered blood pressure or a determination of the initiating factor. It seems conclusive that the cause of the low blood pressure in experiments of the duration reported here in which large masses of the muscle of dogs are traumatized is due to the loss of red blood cells and of plasma into the local injured area. In other words, the initiating agent in the decline in blood volume and blood pressure is certainly the local loss of part of the blood volume into the tissues at the site of injury. In shock produced by some of the other methods, the explanation is more complicated and is not entirely understood. The shock that is associated at times with abdominal operations in patients is an example of this. Complicating factors include the anesthetic and the fact that the patient is usually already ill. The opening of the peritoneal cavity and the manipulation of the organs may be associated with a decline in pressure which is probably neurogenic in origin. Hemorrhage in varying amounts and many other factors may also form part of the picture.

It has been stated that the loss of fluid into the injured area in the experiments in which an extremity was traumatized was sufficient to cause a marked decline in the blood volume and blood pressure. Having determined this point, I was interested in knowing if there are additional factors that are responsible for the alterations observed at autopsy, following trauma, in the tissues of the body other than those at the site of injury. The method chosen for this study consisted of the removal of blood from unanesthetized dogs in such a manner that the blood pressure was maintained at a low level preceding death for as long as possible. Pain was prevented by the use of local anesthesia in the introduction of cannulas into the vessels. Experiments of this type are relatively free from objections, in that general anesthesia is

not used and other complicating factors are excluded. The arterial blood pressure and pulse pressure were considerably lower than normal throughout the experiments, but death occurred without the blood pressure having remained at a low level for more than an hour or two. Despite this fact, the alterations in the tissues in some instances were rather marked. A low blood pressure of longer duration was obtained in other experiments by a combination of the removal of blood and the introduction of blood in such a manner that death was delayed. The alterations in the tissues were more marked in these studies. The latter experiments are open to criticism possibly on the grounds that the blood that was injected may have been responsible for some of the alterations in the tissues. The fact that changes of a lesser degree occurred in the experiments on hemorrhage alone in which no blood was introduced makes this seem unlikely. In several of the experiments, definite evidences of a reaction as a result of the transfusion appeared, and these studies were discontinued. Since changes in the tissues similar to those reported following death from trauma may be produced by hemorrhage alone, it is apparent that the reduction in the blood volume and blood pressure as a result of the local loss of fluid from the blood stream into the injured area may be solely responsible for all of the alterations in the tissues that are observed at autopsy.

The materials carried to the tissues by the blood may be classed as food, water and oxygen. Of these materials, the one that must be supplied continuously is oxygen. It is probably lack of sufficient oxygen that is directly responsible for the changes in the tissues that appear when the blood volume and blood pressure are greatly reduced. Different tissues vary in their resistance to want of oxygen. The central nervous system and particularly the brain withstand a poor supply of oxygen less well than most of the other tissues of the body. Numerous studies by many investigators have dealt with the effects of the partial deprivation of oxygen on the nervous system, and these studies were not repeated in the present investigation. The most marked alterations in the present studies were usually found in the intestinal tract, the liver and the suprarenal glands. Skeletal muscle was essentially normal. Gesell<sup>6</sup> showed that a diminution in the blood volume does not result in an equal decrease in the blood supply to various tissues of the body. Glandular and muscular tissues probably have their supply diminished most.

The general impression was gained in the present experiments that the degree of alterations in the tissues was dependent in the main on

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6. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and of Tissue Abuse in Relation to Secondary Shock, *Am. J. Physiol.* **47**:468, 1919.

the length of time that the blood pressure remained at a low level. That there are other factors than this was shown in other experiments. In some of the experiments on hemorrhage, for example, the arterial pressure and pulse pressure were reduced for the entire time, but the pressure was at a low level for only a short while. Apparently a moderate depression of the systolic pressure with a small pulse pressure for a number of hours may result in changes in the tissues. The production of profound anesthesia of long duration by barbital or ether was associated with changes in the tissues. The diminution of the pulse pressure may have been associated with a sufficient decrease in the blood supply to the organs to cause the alterations. It seems more likely that the anesthetics damage the capillaries directly.

In the care of patients, one rarely encounters as a result of hemorrhage a low blood pressure which persists for several hours. If bleeding occurs to the outside from a large blood vessel, usually early death occurs, or the bleeding is controlled, and the blood volume is augmented artificially or by the withdrawal of fluid from the tissues. If a person bleeds to death within a few minutes following injury, it is only natural that the tissues of the body should appear anemic at autopsy. When large masses of tissues such as the muscles of the thigh are injured, the decline in blood pressure is slower, and the duration of the low blood pressure is longer because the speed with which the fluid escapes is retarded by the size of the vessels and the pressure existing in the tissue spaces. After the pressure in the vessels declines, the escape of fluid is further retarded. Since following trauma the blood pressure usually declines slowly and remains at a low level for a considerable time preceding death, the tissues during this period are partially deprived of blood and oxygen, and changes in them take place. Shock following hemorrhage from a large blood vessel is usually associated with a dilution of the red blood cells in the blood vessels, while shock following trauma to tissues is usually associated with a concentration. When bleeding from a large blood vessel occurs, the fluid that is lost is whole blood. If the bleeding is stopped, fluid from the tissue spaces passes into the blood stream, thereby diluting the red blood cells remaining there. On the other hand, the fluid that escapes into the tissue spaces following trauma to masses of tissues consists in the main of blood plasma. The ratio of red blood cells to plasma is much less than that existing in the blood vessels. Fluid that passes from the tissue spaces into the blood stream continues to be lost through the injured capillaries, and an increase in the concentration of the red blood cells results. It has been shown in the present experiments that hemorrhage alone is frequently associated with an increase in the concentration of the red blood cells if the blood pressure is caused to remain at a low level for



an hour or more. This concentration probably occurs because of the loss of fluid through capillaries that are damaged by the decrease in the flow of blood. It was also shown in the present experiments that the transfusion of blood may be entirely ineffective if the blood pressure has been maintained at a low level by hemorrhage alone. Hence it is to be noted that an increase in the concentration of the blood, a lack of favorable response to the transfusion of blood and capillary congestion and hemorrhage are not peculiar to shock due to trauma, as has been supposed, since these findings may be associated with shock due simply to the removal of blood from a large blood vessel.

Freeman<sup>7</sup> recently reported the results of experiments in which it was found that prolonged vasoconstriction of itself results in a loss of blood from the circulation. He stated, "If we examine all factors which are at present known to produce shock or to aggravate the condition if present, we find that they have one physiological action in common. They are all adequate stimuli for producing hyperactivity of the sympathetic nervous system." Even though vasoconstriction is present, it does not follow necessarily that it is the initiating agent in the production of shock. Hemorrhage, for example, is associated with vasoconstriction and a diminution in the blood volume, but the volume of blood is diminished before the vasoconstriction takes place. A low blood pressure of three hours' duration was produced in some of the present experiments by the injection of acetylcholine, which produces vasodilatation. A great increase in the concentration of the red blood cells occurred, and marked alterations in the tissues were observed at autopsy.

Roome, Keith and Phemister<sup>8</sup> found that the loss of relatively small quantities of blood produced death after a decline in blood pressure had been produced by hemorrhage or trauma to an extremity. It was necessary to remove much larger quantities of blood in order to cause death when a similar decline in blood pressure had been produced by hyperventilation, anaphylaxis, administration of histamine, section of the spinal cord and spinal anesthesia. Confirmation of their results was obtained by a different method in the present experiments. The amount of blood that remained in the pleural and peritoneal cavities after the removal of the organs was determined in the various groups of experiments. The average quantity of blood as expressed in percentage of body weight in the different types of experiments was as follows: (1) control, 5.93; (2) ether control, 4.23; (3) barbitol control, 5.23; (4)

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7. Freeman, H. E.: Decrease in Blood Volume After Prolonged Hyperactivity of the Sympathetic Nervous System, *Am. J. Physiol.* **103**:185, 1933.

8. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, *Surg., Gynec. & Obst.* **56**:161, 1933.

injection of histamine, 3.56; (5) injection of acetylcholine, 3.46; (6) increased intrapericardial pressure, 4.74; (7) hemorrhage (no replacement and various anesthetics), 1.40, and (8) trauma of the leg (various anesthetics), 1.73. The similarity in the results of the experiments on trauma to an extremity and those on hemorrhage is close.

#### SUMMARY

The following were some of the findings in the series of experiments reported here:

1. The production of profound anesthesia for an extended time by the administration of sodium barbital or ether was associated with definite alterations in the tissues of the body. In some instances, hemorrhage into the lumen of the intestinal tract occurred. The alterations were slightly more marked with ether than with barbital.

2. The alterations in the tissues that were found following death from hemorrhage using sodium barbital or ether or procaine hydrochloride in the spinal canal as anesthetics were only slightly less marked than those found following death from trauma when the same anesthetics were used. The blood pressure remained at a low level for a longer time in the experiments in which trauma was produced.

3. A comparison of the results of experiments, performed under sodium barbital or ether or spinal anesthesia, in some of which death was caused by hemorrhage and in others by trauma, shows that the quantity of fluid in the injured extremity in the studies in which trauma was produced was approximately equal in amount to the blood withdrawn in the experiments on hemorrhage.

4. The maintenance of the mean arterial blood pressure at approximately 70 mm. for three hours by the injection of acetylcholine or by increasing the intrapericardial pressure was associated with marked alterations in many of the tissues of the body. The mucous membrane of the intestinal tract became red, and hemorrhage into the lumen of the tract occurred.

5. The removal of blood in small amounts at frequent intervals from animals under local anesthesia in such manner that the blood pressure was at a low level for as long a time as possible preceding death was associated with capillary congestion and dilatation in most of the organs and hemorrhage and necrosis of the cells in some of them. Hemorrhage into the lumen of the intestinal tract was observed in most instances.

6. The maintenance of the blood pressure at a low level for several hours prior to death by the combination of the removal of blood and the introduction of blood was associated with marked alterations in the

tissues. The changes appeared to vary directly with the length of time that the blood pressure remained depressed. The animal's own blood was used for the replacement in these experiments, and coagulation was prevented by defibrinating it or by placing it in a solution of sodium citrate or heparin. There was an increase in the concentration of the red blood cells in more than half of the experiments.

7. In other experiments on dogs in which local anesthesia was used, the blood pressure was reduced by hemorrhage, and it was kept at a fairly constant low level for several hours by removing additional blood or by introducing blood by the direct method from a suitable donor. Death occurred in all of the experiments, despite the fact that slightly more blood was introduced than was removed. The gross and microscopic changes in the tissues were marked. Free blood was present in the lumen of the intestinal tract. There was an increase in the concentration of the red blood cells in all of the experiments.

8. The average quantity of blood remaining in the pleural and peritoneal cavities following the removal of the organs was approximately the same in the experiments in which death was produced by hemorrhage and in those in which death was caused by trauma to an extremity. In the other experiments, larger quantities of blood were recovered from the cavities.

Three of the criteria that are frequently given as differential points between hemorrhage and "traumatic shock" are as follows: (1) Hemorrhage is associated with a decrease in the concentration of the red blood cells, while shock is associated with an increase; (2) death following hemorrhage is associated with an anemic appearance of the tissues, while following shock the tissues show hemorrhage and congestion, and (3) the low blood pressure resulting from hemorrhage is promptly recovered from if a transfusion of blood is given, while shock is not greatly benefited by transfusion. The present experiments show that shock which is associated with an increase in the concentration of the red blood cells, with capillary congestion and hemorrhage in the tissues and with a negative response to the transfusion of blood, can be produced by hemorrhage alone. A prolonged low blood pressure as a result of hemorrhage from a large blood vessel is rarely encountered in patients, because early death or control of the bleeding, with or without the introduction of fluids, usually takes place. On the other hand, one frequently encounters a prolonged low blood pressure which results from trauma to tissues. In this condition, the injury to many small blood vessels allows the escape of red blood cells and of plasma. The loss of fluid and hence the decline in blood pressure are slower than in hemorrhage from a large blood vessel because of the smaller size of the vessels and the greater pressure in the tissues where

the fluid escapes. The results of the treatment of shock due to the loss of blood from a large blood vessel and that due to the loss of fluid from many small vessels in an injured area are different in the early stages in that if the bleeding from the large vessel is stopped, blood introduced into the blood stream will stay there, whereas it is impossible to control entirely the loss of fluid from the many small vessels. If, however, a low blood pressure which persists for several hours results from either of these types of injury, the condition of affairs is more nearly the same in that general injury to the capillaries takes place as a result of the insufficient flow of blood, and fluid introduced into the blood stream will not be retained.

It is to be emphasized that this study is not concerned with a rapid decline in the blood pressure such as that produced by vigorous manipulation of the abdominal organs, by spinal anesthesia or by injury to the central nervous system. Neither is it concerned with postoperative shock, which may be caused by a combination of many factors, such as the disease that prompted the operation, hemorrhage, infection, anesthesia, loss of fluid from the exposed surfaces and dilatation of large areas of capillaries. It is concerned primarily with the decline in blood pressure which is slow in onset and progressive and which was produced in most of these experiments by the slow withdrawal of blood and by trauma to large masses of muscle.

THERAPEUTIC USE OF CONCENTRATED ANTISTREPTOCOCCUS SERUM OF NEW YORK STATE  
DEPARTMENT OF HEALTH

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EARLY INVESTIGATIONS OF STREPTOCOCCUS SERUM

The serum of animals immunized against hemolytic streptococci was early introduced for the treatment of human disease. Marmorek<sup>1</sup> employed a streptococcus of high virulence to immunize horses, asses and sheep. The serum of these animals was then found to possess preventive and curative value in the streptococcic infection of rabbits. Marmorek treated forty-six patients with severe erysipelas by the injection of from 5 to 20 cc. of serum, and all but one made a rapid recovery. He believed that a potent serum could be obtained only by employing for immunization a virulent and toxic strain of the streptococcus.

Subsequent clinical experience with serum therapy in streptococcic infections has resulted in conflicting opinions. Some reports were favorable, but perhaps more were unfavorable. In part, these discrepancies may be ascribed to the use of different serums, but this explanation is not quite adequate. Even today we are unable to explain in a wholly satisfactory manner the variable clinical results.

In some diseases the natural course of the malady, when uninfluenced by therapeutic meddling, tends to follow a more or less definite schedule and to terminate in recovery or in death. In other disorders, the course tends to be variable, and the complications and eventual outcome are lacking in uniformity. Infections with the hemolytic streptococci belong in the latter category. On that account the appraisal of any therapeutic agent for streptococcic infections is made difficult, and any decisive statement in regard to this matter is calculated to promote controversy rather than conviction.

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This work has been made possible by a grant from the Josiah Macy Jr. Foundation.

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1. Marmorek, A.: Le sérum antistreptococcique, *Compt. rend. Soc. de biol.* 47:230, 1895; *Ann. Inst. Pasteur* 9:593 (July 25) 1895.

The preparation of the serum presents difficulties, and the various samples on the market are evidently far from uniform in potency. The methods for testing potency are somewhat unsatisfactory, and the results of titration tests are, as a rule, less definite and less reliable than in the case of such therapeutic serum as that of diphtheria or of tetanus. Apparently much of the streptococcus serum furnished for therapeutic use is comparatively feeble in action.

It is also possible that differences in variety among the hemolytic streptococci may be of significance in this connection. A serum effective against one particular strain may conceivably be without effect on another strain. As early as 1897, Van der Velde<sup>2</sup> employed for immunization of animals a number of streptococcus cultures isolated from various clinical types of streptococcic infection in man, hoping in this way to produce a more effective polyvalent therapeutic serum. It will be noted that this idea is somewhat different from that of Marmorek, who relied on one strain and placed emphasis on high virulence and high toxicity of the culture strain employed. The question is still somewhat controversial. However, the desired improvement in clinical results was not realized, and in the early part of this century serum therapy in streptococcic infections fell into disuse.

#### RENEWED INTEREST IN SERUM THERAPY OF STREPTOCOCCIC INFECTIONS

A reawakened interest in antistreptococcus serum gradually gathered momentum as a result of studies on scarlet fever, particularly because of the promise of practical therapeutic results by the use of serum in this disease. Pioneer work in this field was carried out by Moser<sup>3</sup> and by Savchenko,<sup>4</sup> but this work received little or no attention in the United States until George F. Dick<sup>5</sup> and Gladys Henry Dick presented the

2. Van der Velde, H.: De la nécessité d'un sérum antistreptococcique polyvalent pour combattre les streptococcies chez le lapin, *Arch. de méd. expér. et d'anat. path.*, Paris 9:835, 1897.

3. Moser, P.: Ueber die Behandlung des Scharlachs mit einem Scharlachstreptokokkenserum, *Wien. klin. Wchnschr.* 15:1053, 1902; Ueber antistreptokokken serum bei Scharlach, *Berl. klin. Wchnschr.* 40:13, 1903.

4. Savchenko, I. G.: Opregoloolenii protivovskarlatinnoi sivorotki (Preparation of Antiscarlatinal Serum), *Russk. vrach* 4:797, 1905.

5. Dick, G. F., and Dick, Gladys H.: Experimental Inoculations in Scarlet Fever, *J. A. M. A.* 77:782 (Sept. 3) 1921; Experimental Scarlet Fever, *ibid.* 81:1166 (Oct. 6) 1923; A Skin Test for Susceptibility to Scarlet Fever, *ibid.* 82:265 (Jan. 26) 1924; The Etiology of Scarlet Fever, *ibid.* 82:301 (Jan. 26) 1924; Scarlet Fever Toxin in Preventive Immunization, *ibid.* 82:544 (Feb. 16) 1924; Scarlet Fever Antitoxin, *ibid.* 82:1246 (April 19) 1924; Prevention of Scarlet Fever, *ibid.* 83:84 (July 12) 1924; Scarlet Fever, *Am. J. Pub. Health* 14:1022, 1924.

results of their investigations. These authors appear to have induced scarlet fever by the inoculation of pure cultures of streptococci into the throats of volunteer human subjects. They have been able to obtain a toxic filtrate of broth cultures which they employ by injection into the skin as a test for susceptibility to scarlet fever. With an amount equal to 1,000 skin test doses of toxic filtrate they were able to cause transient symptoms of mild scarlet fever in susceptible adults. They also produced a concentrated immune horse serum and found that an amount of this antitoxic (immune) horse serum sufficient to neutralize 20,000 skin test doses of toxin constitutes an effective therapeutic dose for scarlet fever. In a satisfactory serum the volume of this therapeutic dose does not exceed 20 cc. Given early, in adequate dosage, they found that it shortens the course of scarlet fever and reduces the number of complications and sequelae. When injected into the skin of a patient in the florid stage of scarlet fever, this serum is able to bring about a blanching of the cutaneous erythema which is apparently similar in all respects to the blanching obtained by the analogous use of serum from a person recently convalescent from scarlet fever. This phenomenon furnished a clearly recognizable proof of some protective property in the serum.

These observations served to encourage the renewal of efforts to produce antistreptococcus serum, and attempts to extend the field of therapeutic application to other diseases than scarlet fever followed as a matter of course. Erysipelas may be particularly mentioned. Clinical experience has not been uniformly favorable in the serum therapy of either scarlet fever or erysipelas, but the favorable reports have been sufficiently numerous to encourage the continued production of serum for the treatment of these conditions.

However, even as late as 1923, there were commanding voices raised against the use of antistreptococcus serum. Thus Gay,<sup>6</sup> in July 1923, was able to say: "There is nothing approaching acceptable evidence of the successful treatment by serum of any of the streptococcal infections, except possibly in the complications of scarlet fever. Many definite reports of failure to procure results are available." It should be noted, however, that this author seems to have modified somewhat his position on this question in recent years. In 1930, he<sup>7</sup> reported that experimental streptococcic pleurisy of rabbits could be prevented in about 20 per cent of the cases by the use of a potent antistreptococcus serum, and that such a serum combined with exudate cells afforded a high degree of protection.

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6. Gay, F. P.: *The Use of Antiserums in the Treatment of Diseases*, J. A. M. A. **81**:284 (July 28) 1923.

7. Gay, F. P.: *The Grades of Resistance and Immunity to Bacteria*, Tr. A. Am. Physicians **45**:321, 1930.

## SERUM THERAPY IN STREPTOCOCCIC BACTEREMIAS

In France, a renewed interest in antistreptococcus serum seems to have been initiated by Vincent<sup>8</sup> in 1929. Successful treatment of streptococcic bacteremia by the use of Vincent's serum has been reported by several authors<sup>9</sup> since 1929. The dosage of his serum is 100 cc. per day; the administration is started as soon as the diagnosis can be made, and the amount is diminished only as the infection recedes. According to Vincent, serotherapy should be continued until all symptoms have disappeared and for two or three days after complete cessation of fever.

In England, Benson<sup>10</sup> and Rankin observed one hundred and fourteen cases of puerperal sepsis, all with hemolytic streptococci demonstrated by blood culture. The puerperal antistreptococcus serum of Burroughs, Wellcome and Company was given to 20 patients, and the concentrated scarlatinal streptococcus antitoxin of the same company was administered to 37 patients. The total dosage varied from 100 to 330 cc. The mortality in the group treated with serum was 75 per cent, and in the control group of fifty-seven patients without serum treatment the mortality was 68 per cent. Serum reactions were quite distressing, especially after intravenous administration. These observations do not favor the use of antistreptococcus serum.

Penfold<sup>11</sup> and Corkill, in Australia, observed steady improvement and eventual recovery in a patient with streptococcic septicemia treated with serum. These authors recommend that white mice be inoculated with the blood culture from the patient and then be given injections of each available kind of antistreptococcus serum. Death of the control mice and survival of the mice treated with serum serve to indicate a specific therapeutic value of the particular serum. In this way one may select the best available serum for the particular patient.

In the United States, recent experience seems to have been more favorable to serum therapy in streptococcic infection. J. H. Park Jr.<sup>12</sup>

8. Vincent, H.: Sur les résultats thérapeutiques donnés par un nouveau sérum antistreptococcique, *Compt. rend. Acad. d. sc.* **188**:1348 (May 27) 1929.

9. Hubert, C.; Girard, L., and Hemon: Deux cas de septicémie à streptocoques guéris par le sérum antistreptococcique de Vincent, *Bull. Acad. de méd., Paris* **104**:405 (Nov. 25) 1930. Vincent, H.: La septicémie à streptocoques. Son traitement par un nouveau sérum antistreptococcique, *ibid.* **105**:735 (May 5) 1931. Courty, M. L.: Septicémie à streptocoque traitée et guérie par le sérum de Vincent, *ibid.* **106**:89 (July) 1931. Canuyt, G.: Streptococcus Septicemia of Pharyngeal Origin; Cure Following Therapy by Fixation Abscess and Vincent's Antiserum, *Strasbourg méd.* **92**:560 (Sept. 15) 1932.

10. Benson, W. T., and Rankin, A. L. K.: Treatment of Puerperal Septicemia with Antitoxic Serum, *Lancet* **1**:848 (April 22) 1933.

11. Penfold, W. J., and Corkill, O. B.: Septicemia with Recovery, *M. J. Australia* **1**:341 (March 17) 1928.

12. Park, J. H., Jr.: The Serum Treatment of Acute Streptococcic Infection of the Respiratory Tract of Infants and Children, *M. Rec. & Ann.* **24**:581, 1930.



treated forty-one children with acute streptococcic infection of the respiratory tract by injecting polyvalent antistreptococcus serum together with therapeutic scarlet fever antitoxin. When this treatment was administered before the fifth day it was followed by complete recovery without sequelae in every case. These results presented a marked contrast when compared with those in the other children afflicted in the same outbreak who did not receive the serum.

Jopson<sup>13</sup> and Eiman observed forty-three cases of infection of the blood stream with hemolytic streptococci. In twenty no serum was given and in four the injections were either inadequate or administered too late, making a total of twenty-four cases with nineteen deaths and five recoveries. The survivors had (1) mastoiditis with sinus thrombosis and high fever for forty days; (2) high fever for five days following mastoidectomy, (3) abortion with high fever for thirty days and (4) cellulitis of the hand treated by incision and drainage (two cases). Nineteen of the patients received antistreptococcus serum in total amounts between 150 and 750 cc. Of these, fifteen recovered and four died. The four fatalities were due to (1) abortion with multiple abscesses in the myometrium and thrombosis of the ovarian and renal veins, (2) cellulitis of the leg, (3) abortion with clinical peritonitis (no necropsy) and (4) abortion and ruptured uterus with generalized peritonitis (necropsy). The authors distinguish between the shower type of septicemia and massive invasion of the blood stream. They also discuss the significance of other factors, such as the state of the various organs, maintenance of water balance, nutrition, the proper use of transfusions and the surgical treatment of primary and secondary foci. Hypersensitiveness to horse serum could not always be overcome even after seven or more carefully graded doses of the serum, and on that account these authors occasionally employed bovine serum. They regard the streptococcus serum as of decided value.

#### POLYVALENT SERUM PROBABLY UNNECESSARY

Amoss, Persons and Hansen-Prüss<sup>14</sup> treated five patients with antistreptococcus serum, all of whom were critically ill with streptococcic pneumonia and not expected to live. The serum was that of the New York State Board of Health and a commercial brand. Both seemed to produce beneficial results. All five patients recovered, and all suffered from serum sickness. These authors also demonstrated the protective effect of the serums on mice.

13. Jopson, J. H., and Eiman, J.: The Serum Treatment of Bacteremia Due to Hemolytic Streptococcus, *Ann. Surg.* 92:910 (Nov.) 1930.

14. Amoss, H. L.; Persons, E. L., and Hansen-Prüss, O. C.: Serum in the Treatment of Streptococcus Pneumonia, *Tr. A. Am. Physicians* 46:208, 1931.

In discussing this paper, Wadsworth stated that a serum produced by immunizing horses with the Dochez streptococcus strain N.Y. 5 had been found to protect against between 75 and 80 per cent of five hundred strains of streptococci tested.

In some of his later publications, Wadsworth<sup>15</sup> questioned the recognition of a specific streptococcus of scarlet fever. The serum produced by immunizing a horse with the Dochez strain N.Y. 5 from a case of scarlet fever was found to neutralize the toxins of 65 per cent of pathogenic streptococci, regardless of their origin. The serum of an animal immunized by the use of streptococcus from erysipelas gave analogous results. Wadsworth does not regard the toxins of these different bacterial strains as identical, and he recognizes differences in the serums. However, he considers scarlet fever not as a specific infectious disease but rather as a manifestation of streptococcic infection which is in varying degree characteristic.

Comparative tests in the laboratory of the New York State Department of Health during a period of five years have shown that relatively few samples of streptococcus serum possess a potency as high as 400 units per cubic centimeter. Only when the Dochez streptococcus strain N.Y. 5 has been employed has it been possible to get a horse serum with a potency of from 600 to 800 units per cubic centimeter. Most of the samples of streptococcus serum in general use continue to approximate only minimum standards of potency.

Wadsworth expressed the belief that the interaction between streptococci and the body defenses is of a complex nature, such that various clinical manifestations appear as a result of infection of different hosts with the same identical strain of streptococcus. Furthermore, the influence of the therapeutic serum is also complex and not well understood. Evidently its effect is influenced by other defense mechanisms of the animal host which themselves are still obscure. He concludes that streptococcus serum has a demonstrated value in the treatment of scarlet fever, erysipelas and streptococcic sore throat and an apparent but not clearly proved value in more severe streptococcic infections, even those with bacteremia. He expects further light to be shed on the subject of streptococcus serum therapy as a result of clinical experience with a newer concentrated serum of high potency that titrates approximately 3,000 units per cubic centimeter. This serum has recently been produced in his laboratory at Albany.

15. Wadsworth, A. B.: Studies of the Streptococci and Anti-Streptococcus Serum in Scarlet Fever, *Compt. rend.-Congr. Internat. de microbiol.* **1**:308, 1931; Serum Therapy: Its Value in Pneumonia, Meningitis, Scarlet Fever and Other Streptococcus Infections, *J. A. M. A.* **99**:204 (July 16) 1932; Recent Advances in the Serum Therapy of Pneumonia, Meningitis, Scarlet Fever and Other Streptococcus Infections, *Tr. A. Am. Physicians* **47**:161, 1932; Serum Therapy of Streptococcus Infection, *Canad. Pub. Health J.* **24**:1 (Jan.) 1933.

THE CONCENTRATED SERUM OF THE NEW YORK STATE  
DEPARTMENT OF HEALTH

Late in 1931, Dr. Augustus B. Wadsworth, director of the division of Laboratories and Research, New York State Department of Health, made available to us, with certain restrictions as to its use, an almost unlimited supply of the newer, high titer, concentrated serum, with a potency of from 2,500 to 3,000 units per cubic centimeter.

According to information received from Dr. Wadsworth, the serum is obtained by immunization of horses, first with living streptococci of the Dochez<sup>16</sup> strain N.Y. 5 injected into a mass of agar previously introduced in a fluid state under the skin of the animal and allowed to harden there (Dochez agar-culture method). Later, subcutaneous doses of toxic filtrate, supplemented by further injections of living organisms by the agar-culture method, are given. The treatment of the horses is continued for from one to two years or even longer. Eventually the serum of the horse has a potency of from 800 to 900 units per cubic centimeter. Concentration is accomplished by precipitation with ammonium sulphate and further purification by iso-electric precipitation of the water-insoluble globulin, giving a final potency of from 3,000 to 3,600 units per cubic centimeter.

The opportunity to test this serum in serious streptococcic infections was welcomed by us because we were occasionally placed in a somewhat difficult position when asked to help in the treatment of septic patients. Subsequent to a certain measure of success attained in the bacteriophage<sup>17</sup> treatment of bacteremias due to staphylococci and to colon bacilli, some of our clinical colleagues appealed to us for assistance when they were confronted with cases of septic infection, regardless of the specific nature of the infecting microbe. Not infrequently the important infectious agent would prove to be the hemolytic streptococcus, an organism against which we did not possess any potent bac-

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16. Stevens, F. A., and Dochez, A. R.: *The Study of Hemolytic Streptococci Associated with Scarlet Fever*, Proc. Soc. Exper. Biol. & Med. **21**:39, 1923. Dochez, A. R., and Sherman, L.: *Significance of Streptococcus Hemolyticus in Scarlet Fever: Preparation of a Specific Antiscarlatinal Serum by Immunization of Horse to Streptococcus Hemolyticus-Scarlatinae*, J. A. M. A. **82**:542 (Feb. 16) 1924; *Studies Concerning the Significance of Streptococcus Haemolyticus in Scarlet Fever*, Proc. Soc. Exper. Biol. & Med. **21**:184, 1924. Dochez, A. R., and Stevens, F. A.: *Studies on Biology of Streptococcus: Agglutination and Absorption of Agglutinin with Streptococcus Scarlatinae*, J. Exper. Med. **40**:253, 1924; *Studies on Biology of Streptococcus; Occurrence of Streptococcus Scarlatinae in Convalescence and in Complications of Scarlet Fever*, *ibid.* **40**:493, 1924.

17. MacNeal, W. J., and Frisbee, F. C.: *Bacteriophage as a Therapeutic Agent in Staphylococcus Bacteremia*, J. A. M. A. **99**:1150 (Oct. 1) 1932. MacNeal, W. J.; Frisbee, F. C., and Applebaum, Martha: *III. Use of Bacteriophages in the Treatment of Colon Bacillus Septicemia*, Arch. Surg., to be published.

teriophage. It became a source of satisfaction for us to have available a streptococcus serum for use in such patients. At first the invitation to employ bacteriotherapeutic measures came only after the condition of the patient appeared to be quite hopeless. Later it became possible for us sometimes to use the serum even in patients who seemed to have a good chance to survive without it. More recently it has been possible to use the serum in still earlier stages of streptococcic infection in order to forestall threatened extension of the infection and consequent mutilating operative procedures.

The case histories to be presented in the succeeding papers of this series have not been selected with the purpose of proving any thesis. They represent our total experience in the use of the concentrated streptococcus serum of the state laboratory during a period of approximately two years. It is not certain that the most effective methods of employing serum therapy in streptococcic infections have yet been ascertained. We are convinced, however, that the serum is being more intelligently and more effectively employed in our more recent cases than in the earlier ones of our series. We are also certain that the serum therapy of streptococcic infections is now held in much higher esteem by our clinical associates than it was in 1931.

#### SUMMARY AND CONCLUSIONS

1. Serum therapy of streptococcic infections has been a controversial subject almost since the description of the first streptococcus serum by Marmorek in 1895.
2. After a period of disfavor and disuse, interest in streptococcus serum was revived by its somewhat successful application in the treatment of scarlet fever and of erysipelas.
3. While the classification of the hemolytic streptococci is still confused, there is no valid reason for distinguishing between therapeutic serums for different clinical types of streptococcic infection.
4. The most potent antistreptococcus serum now available appears to be the concentrated serum of the laboratory of the New York State Department of Health.

# A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 696)

## BLADDER

*Tumors Among Dye Workers.*—Anderson<sup>24</sup> stated that occupation is a causal factor in the development of vesical tumors among workers in aniline dyes. The duration of occupation and not the age of the patient is the determining factor in the development of such tumors. The familial history is apparently an unimportant factor. Neither positive nor negative symptoms and signs are conclusive evidence of the presence or absence of vesical tumors among these persons. A positive diagnosis of such a tumor can be made only by early and periodic cystoscopic examinations.

Gehrmann<sup>25</sup> stated that vesical tumors occur more commonly among dye workers than in other persons and that in his experience such tumors occurred among 4.5 per cent of the former. The combined experiences of the dyeing industries of Germany, Switzerland, England and America indicate that aniline, alpha and beta naphthylamine and benzidine probably are the etiologic compounds. Vesical tumors may appear at any time after two years' exposure, and removal of the worker from the dye operation does not eliminate the possibility of the future development of the growth. The adoption of a completely closed and properly ventilated process, together with careful medical supervision

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24. Anderson, L. W.: Incidence, Symptoms and Signs, Results of Survey, J. Urol. **31**:148 (Feb.) 1934.

25. Gehrmann, G. H.: The Carcinogenetic Agent-Chemistry and Industrial Aspects, J. Urol. **31**:126 (Feb.) 1934.

and protection will eliminate the hazard, but these methods will require many years of active enforcement and must continue so long as the compounds are made.

Gay<sup>26</sup> stated that the pathologic characteristics of tumors of the bladder among dye workers are not essentially different from those of tumors of unknown origin. The tumors are single or multiple, papillary or sessile, infiltrating or noninfiltrating, ulcerating or nonulcerating; there may also be any combination or sequence of these characteristics. An analysis of 124 of the approximately 200 cases reported from various German sources indicates that the incidence of carcinoma is about twice that of papilloma. The occurrence of nonepithelial neoplasms is rare. In the cases reported papillomas are more often single, and carcinomas are more often multiple. Thirty-seven tumors were situated on the trigon, and 16 were found elsewhere in the bladder. In this series tumors situated elsewhere than on the trigon appeared to be more malignant than those situated at the base of the bladder. Although the tumor may invade the tissues of the pelvic cavity, metastasis is extremely rare. There are many records of submucous hemorrhages, localized areas of hyperemia or cystitis in which tumors developed later.

Gay gave data on 17 tumors of the bladder occurring among dye workers, which had been examined microscopically. Seven were papillomas of grade 1. The remaining 10 lesions were classified as follows: 4, papillary carcinoma of grade 2; 1, carcinoma of grade 3; 1, carcinoma of grade 4; 3, coexistent papilloma and carcinoma; 1 was diagnosed as carcinoma but not graded. The multiple tumors were all carcinomas. Seven of the single tumors were papillomas, and 3 were carcinomas. In 8 cases the tumors were not preceded by symptoms.

Washburn<sup>27</sup> reported that 23 men, all engaged in the manufacture of dyestuffs in the United States, had been treated for tumor of the urinary bladder. Eleven of these men had single tumors which were treated through the cystoscope by fulguration with the bipolar current, and 7 had multiple tumors which were treated in the same manner. Two patients in this group have had new lesions in a different situation. Open operation was performed in 5 cases; 2 patients of this group had a single tumor, graded 3 and 4, respectively. The remaining 3 lesions were multiple; 2 were graded 3 or 4, and 1 was clinically malignant but unfavorable for biopsy. There have been no deaths in the series.

26. Gay, D. M.: Pathology of Anilin Tumors of the Bladder, *J. Urol.* **31**: 137 (Feb.) 1934.

27. Washburn, V. D.: Treatment of Anilin Tumors of the Urinary Bladder, *J. Urol.* **31**:155 (Feb.) 1934.

*Tumors.*—Kretschmer<sup>28</sup> and other members of the Committee on Carcinoma Registry reviewed reports of 902 cases of epithelial tumor of the bladder submitted to the Carcinoma Registry of the American Urological Association. The sex incidence in this series is approximately 76 per cent males and 23 per cent females. The peak age incidence was from 55 to 59 years; 62 per cent of the patients were between the ages of 50 and 69 years. Sixteen epithelial tumors of the bladder occurred among aniline dye workers. A family history of carcinoma was of no apparent significance in this series of cases of carcinoma of the bladder.

Tumors involving the lateral walls, trigon and neck of the bladder constituted 76.6 per cent of all the tumors in this series. Less than half of the neoplasms in these situations were highly malignant, whereas 3 of every 4 tumors of the vault of the bladder were of grades 3 or 4. The site of the growth has little apparent relation to the prognosis except when the vault is involved, in which case the prognosis for five year cures is 18.7 per cent.

Of the total number of epithelial tumors, 643 were single and 250 were multiple. Only 1 of every 3 multiple tumors was highly malignant, whereas half of the single tumors were of grades 3 or 4. Forty-five per cent of the tumors in this series were larger than 5 cm. in diameter when first observed. When the tumor was less than 2 cm. in diameter the results were greatly improved. Metastasis was present in approximately 10 per cent of the cases in this series.

Recurrence followed treatment in 46.2 per cent of the cases. Detailed observations were made at necropsy in 79 of the 902 cases. On microscopic examination approximately half of the tumors were found to be infiltrating. In 5 per cent of the cases tumors of more than one type were found. Hematuria was the initial symptom in 63 per cent of the cases, and it was discovered on examination in 76 per cent of the cases. Only 10.8 per cent of the patients were completely examined and the diagnosis established within one month. In 48 per cent of the cases in the series the diagnosis was delayed more than one year. Loss of weight constituted a major complaint in slightly more than one fourth of the cases.

Careful preoperative preparation of patients with carcinoma of the bladder should be observed as a means of reducing the operative mortality. More than one third of the patients were found to have serious impairment of renal function. Cystoscopic examination, biopsy and

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28. Kretschmer, H. L.; Barringer, B. S.; Braasch, W. F.; Dean, A. L.; Ferguson, R. S.; Keyes, E. L., and Smith, G. G.: *Cancer of the Bladder; a Study Based on 902 Epithelial Tumors of the Bladder in the Carcinoma Registry of the American Urological Association*, J. Urol. 31:423 (April) 1934.

roentgen examination are the principal means of diagnosis, and they were shown to be highly accurate in this series. The standard methods of treatment were resection, fulguration and irradiation. Of 349 patients observed for five years or more, 33.24 per cent were alive at the end of that period.

Keyes<sup>29</sup> presented a report on case histories, the basis of which constituted a continuation of the histories of 31 patients with vesical tumor treated by suprapubic implantation of metal capsules containing radium. These 31 cases have been reported previously and the method of operation described. They are the first 31 cases in which operation was performed by Keyes' method. The operations were performed between December 1925 and March 1928. The results five years after these operations are quite gratifying in spite of the fact that 4 cases have been included (4, 15, 16 and 17) in which initial treatments were made by resection or by implantation of radium using less satisfactory methods; 2 with glass seeds and 2 with steel needles containing radium element. The 4 patients have died of carcinoma. In the previous report 2 deaths from operation were recorded; 1, three days after suprapubic implantation of radium; the other, caused by ileus, following resection of the bladder for persistent tumor of the vault after repeated implantation of radium had failed. In the previous report results were tabulated after dividing the types of papillomas into four groups: grades 1, 2, 3 and 4.

Keyes stated that it is interesting to compare the prognostic accuracy of the older methods of more or less combined clinical and pathologic malignancy with the modern grading. According to the older classification 8 tumors were graded 1 and 2. Only 1 (12.5 per cent) of these patients died. Eleven tumors were of grade 3; 2 patients died following operation, and 3 died later of carcinoma, making a mortality of nearly 50 per cent. One of these patients lived three and a half years from the time of the original treatment. Thirteen of the 14 patients died of carcinoma clinically graded 4.

Keyes commented that all epithelial tumors of the bladder graded 1 or 2 should be regarded as curable and treated by fulguration, implantation of radon or cystectomy unless the patients were moribund or unless for other reasons operation could not be performed. For lesions of grade 3 the prognosis is poor. He reported that only 23 per cent of such lesions were controlled for five years. Most of the deaths from carcinoma occur in the first two years. The prognosis for lesions of grade 4 is even worse. One patient had remained at work and apparently was well for six years, when he suddenly died of carcinoma.

29. Keyes, E. L.: Five-Year Results of Suprapubic Radium Implantation into Bladder Tumors, *Tr. Am. A. Genito-Urin. Surgeons* 26:207, 1933.



Keyes reported 37 implantations of radon with but 1 postoperative death. Postoperative spasms which follow implantation of glass seeds do not occur unless more than twenty radon seeds are implanted. Twenty-seven of the operations were followed by no more discomfort than is to be expected after cystotomy. The 6 patients who required more than one operation submitted to the second operation without comment. Resection is not applicable to tumors about the trigon or vesical neck, although tumors in these sites present no peculiar difficulties to the implantation of radon. Ureteral reimplantation does not have to be considered. The operative mortality is much lower, and the stay in the hospital is so much shorter that it pays for the radium. In this series drainage was carried out in 11 cases, and in the 26 cases in which suture was made without drainage, wounds broke open in 11. In the 15 cases in which leakage did not occur, the average postoperative stay of the patients in the hospital was fifteen days; in the other cases the postoperative fistula remained open on the average for twenty-three days. Keyes stated that it is to be hoped that the permanency of cure with radium is no longer questioned.

Ferguson<sup>30</sup> stated that it had been his privilege to study annually the registry of vesical tumors and to report the contents of it to the American Urological Association. Last year he found 600 cases in the registry, in 154 of which treatment had been given more than five years previously. The figures for five year survivals for each grade at that time corresponded closely to those reported by Keyes, being 72 per cent for grade 1, 43 per cent for grade 2, 24 per cent for grade 3 and 4 per cent for grade 4. This year there are reports in the registry of more than 600 tumors, and the comment that the rate of growth of this registry to date has exceeded the rate of growth of any other registry of national scope is interesting.

Graves and Militzer<sup>31</sup> stated that metastasis to bones from carcinoma of the bladder is more common than is generally supposed. Metastasis may be of slight extent or widespread. Aside from the pelvis there seems to be no particular predilection for any bones. A search for evidence of metastasis must, therefore, be thorough. One case of carcinoma of the bladder with metastasis to the lungs, liver and right fourth rib, histologically proved, is presented. In addition, 4 cases of carcinoma of the bladder with roentgenologic evidence of metastasis to bone are reported. Osseous metastasis from carcinoma of the bladder is usually of the osteoclastic type, although some cases of carcinoma of the bladder also show osteoplastic changes. Two cases

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30. Ferguson, Russell, in discussion of Keyes,<sup>29</sup> p. 227.

31. Graves, R. C., and Militzer, R. E.: Bone Metastases from Carcinoma of the Urinary Bladder, *Tr. Am. A. Genito-Urin. Surgeons* 26:185, 1933.

of carcinoma of the bladder revealing changes in bone suggestive of Paget's disease are reported. Great caution must be observed in condemning a case as inoperable because of associated lesions in the bone.

Nicholls<sup>32</sup> stated that papillomas of the bladder do not tend to metastasize, and if extension does take place it is usually by direct spread to the pelvic tissues or by lymphatic structures to the preaortic glands. Discontinuous metastasis of a benign vesical papilloma is extremely rare, and the widespread skeletal deposits so common in prostatic carcinoma are almost unknown in vesical malignancy.

Nicholls reported a case of apparently benign, transitional cell papilloma of the bladder with multiple skeletal tumors of the same type of growth. The vesical tumor, which on section proved to be a benign papilloma, had been excised by cautery. Three years later the patient returned because of pain and swelling in the right knee. Some hematuria had occurred in the interval and on the posterior wall of the bladder there was a recurrence of the villous tumor, which was removed suprapubically. Ten days later roentgenograms revealed destruction and calcification of the right femur and tibia. Following arthrotomy for biopsy, the tumor of the knee increased, and a mass appeared in the right iliac fossa. The patient died one month after cystotomy had been performed. Extensive metastasis of a transitional cell papilloma similar to the one in the bladder was found in the lungs, ribs, pelvis, right femur and tibia. Sections of all these tumors revealed regular papillary processes in each case, with cells regular in shape and size and no mitosis. Ossification was present in the sections taken from the bony tumors. Section of the vesical wall in the region of the removed tumor gave no evidence of neoplasm.

This case is singular in that the vesical tumor was benign both clinically and microscopically. A tumor removed three years later was single and noninfiltrating, and extensions could not be found in the vesical wall at postmortem examination. The bony deposits were likewise microscopically not carcinomatous, although their growth was rapid and destructive.

Nicholls speculated as to the mode of entry of these cells into the blood stream and concluded from the clinical history that it was independent of either operation. He compared the picture to the multiple thyroid metastasis seen in malignant adenoma of the thyroid gland, which may erode blood vessels and give rise to distant metastasis early in its career when it is small and confined to its capsule, and thus clinically benign.

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32. Nicholls, M. F.: A Case of Vesical Papilloma with Widespread Metastases, *Brit. J. Surg.* 21:108 (July) 1933.

*Stones.*—Adrian<sup>33</sup> reported the remarkable case of a woman aged 50 in whom calculi had taken an extraordinary course from the gall-bladder to the urinary bladder and had been expelled through the urethra. Only 7 similar cases, all occurring between the years 1836 and 1897, have been reported in the literature. Six of these patients were women, and the sex of the seventh was not indicated. The case reviewed by Adrian was first observed in 1919, and the patient has never been lost sight of since. For nine months the patient had expelled through the urethra at least one hundred stones composed of pure cholesterol, forty-eight of which she had saved and turned over to Adrian for study. The stones were of different sizes and shapes, but all were characterized by extreme lightness of weight; these forty-eight stones, which nearly filled a wine glass, weighed altogether only 21 Gm. and floated when placed in water. Most of them were gray, smooth and shiny, with faceted surfaces. However, on one occasion, a stone of an entirely different appearance, yet of the same chemical character, arrived in the urethra; after several days of intermittent urinary retention, culminating in complete retention for sixteen hours, the stone was removed at operation. Cystoscopy revealed a brown rounded calculus, approximately the size of a walnut, with a corrugated surface without facets, lying in a rather unusual position in the left side of the bladder, attributed by Adrian to deformation of the floor of the bladder. In the course of extraction the stone unfortunately was broken to some extent, leaving, however, one large fragment and several small ones that could be patched together; reconstruction of the stone showed that it had been cone-shaped, about 13 mm. in diameter at its base and 12 mm. in height; its weight was 35 Gm. Because of bleeding, cystoscopy could not be carried out for a week; when it was carried out, however, it revealed an empty bladder, the mucosa of which showed no signs of acute inflammation. The ureteral orifices appeared like large slits in the middle of numerous prominences of the hypertrophied vesical musculature. In the supero-anterior part of the cavity, above the "air-bubble," in the middle, Adrian discovered a diverticulum the size of a large almond (about 1 cm.) with its greater diameter running horizontally. Its margins were irregular, and it appeared to be empty.

From that time on the patient never had any further vesical trouble, and her restoration to health caused her to refuse cystography, which might have revealed the exact site of the diverticulum. She did, however, consent to insufflation of the colon, which revealed that the entire transverse colon passed in front of the liver, which was strikingly ptosed. The chemical analysis of the stones showed them to be typical biliary calculi.

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33. Adrian, Charles: *Calculs biliaires dans la vessie d'une femme*, Bull. Soc. franç. d'urol. **37**:386 (Dec. 18) 1933.

Despite ptosis of the liver, it is impossible to assume the existence of a direct communication between the gallbladder and the urinary bladder as the result of simple inflammatory adhesions of the walls of the two organs. Such a communication, if it ever took place, was the result of the interposition of a more or less latent focus of peritonitis. But there is another passage that the calculi may have made use of to reach the bladder, namely, the urachus, after the establishment of an adhesion between the gallbladder and a persistently patent urachus. Among the seven cases found in the literature, two were of this kind (Koestlin, Kroenlein), as was clearly revealed at necropsy. It appears that from 1893 on, when the patient had her first accouchement, up to the spring of 1918, the calculi had remained either in the gallbladder or in the urachus, while they formed a more or less closed cavity separated from the bladder. Not until this had occurred did the patient discharge successively the one hundred or more stones of which forty-eight were saved. That each group of stones which was passed had not remained long within the bladder is shown by the results of chemical examination, and the same is true of the last stone, the appearance of which was different. The really strange occurrence in the case is that after extraction of this last stone, too large to be evacuated spontaneously, a silent cure took place, the gallbladder having emptied itself completely, without causing infection of either the liver or the bladder.

*Hemorrhage.*—Boyd<sup>34</sup> stated that sudden, severe hemorrhages into the unopened bladder are usually best treated by emptying the bladder of clots through suitable urethral instruments and then using quite hot irrigations. Electrocoagulation of the bleeding points is sometimes necessary, and occasionally even suprapubic cystotomy may be required. In elderly or anemic patients radical measures should be instituted without too much delay when the hemorrhage is not readily controlled, especially if ample facilities for transfusions of blood are not available for immediate use.

One of Boyd's patients had a hemorrhage into the bladder following an unsuccessful attempt at urethral catheterization, another hemorrhage several days later, which stopped when the bladder was opened suprapubically, and a third hemorrhage a week later, which stopped when the patient was given a spinal anesthesia to permit reexamination of the bladder. Since no visible source of bleeding could be found at cystotomy and since the patient had a fairly large, benign hypertrophy of the prostate gland, Boyd concluded that the hemorrhage was from the veins which ran in the mucosa that covered the intravesical portion of the prostatic hypertrophy. In this instance these veins may have

34. Boyd, M. L.: Severe Hemorrhage into the Bladder, *Am. J. Surg.* 22:203 (Nov.) 1933.

been unusually engorged by an obstruction to the venous circulation of the bladder, which it appears could have been caused by an extensive, acute abscess of the appendix which preceded the first hemorrhage by about seven weeks. Unexplained irritation had also appeared just after the appendical abscess was opened and had produced pains in the region of the prostate gland, resulting in spasms of straining to urinate and defecate. These spasms recurred at varying intervals of hours or days and in varying severity for several months, and they were worse during and preceding the hemorrhages. Subsequent examination of the urethra, bladder, rectum and abdomen did not reveal the presence of other changes that could account for the symptoms and the hemorrhages.

*Gangrene.*—Stirling and Hopkins<sup>35</sup> reviewed 207 cases of gangrene of the bladder, and reported 2 cases of their own. They stated that in any form of severe, chronic cystitis, the possibility of gangrene should be borne in mind and drainage instituted as early as possible. Gangrene of the bladder occurs more commonly than is suspected, because of failure in diagnosis and in obtaining necropsy. Retention of urine and the presence of infection are the chief predisposing factors. Treatment, if instituted early, may result favorably even in the presence of severe necrosis. Palliative treatment may be tried in females, but early drainage by cystotomy offers the best prognosis in males.

*Pyo-Urachus.*—Stevens<sup>36</sup> reported a case of pyo-urachus which differed from most cases of inflammation of the urachus in that there was no opening leading to the umbilicus or to the bladder; the urachus had not retracted downward as usual but remained attached to the umbilicus. The urachus had remained patent at its upper portion, as proved by the islands of epithelium found. Therefore, the urachus had apparently become merely a cord of smooth muscle and fibrous tissue at the lower end, with no sign of epithelium or of a lumen. The inflammation was confined to the upper part of the urachal structure, without involvement of the vesical end.

#### PROSTATE GLAND

*Prostatectomy.*—Harris<sup>37</sup> summarized his experience over a period of five years with his original method of prostatectomy with closure. There have been some minor though important alterations in the technic. The essential features of this operation, which is not to be used by the

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35. Stirling, W. C., and Hopkins, G. A.: Gangrene of the Bladder: Review of Two Hundred and Seven Cases: Report of Two Personal Cases, *J. Urol.* **31**:517 (April) 1934.

36. Stevens, A. R.: Pyo-Urachus, *Tr. Am. A. Genito-Urin. Surgeons* **26**:13, 1933.

37. Harris, S. H.: Prostatectomy with Closure: Five Years' Experience, *Brit. J. Surg.* **21**:434 (Jan.) 1934.

surgeon who only occasionally performs a prostatectomy, are: (1) immediate and complete control of hemorrhage by suture, (2) reformation of the prostatic urethra by a trigonal-capsular suture, (3) obliteration of the prostatic cavity by this suture and additional anterior transverse oblitative suture and (4) complete closure of the bladder and abdominal wound. The last-mentioned feature, although a valuable asset, is more of a comfort and convenience to the patient than a vital factor in the final outcome. If the bladder is not completely closed postoperative drainage is of short duration and of no consequence as compared to that in other methods of suprapubic prostatectomy.

Careful attention to all details are essential for success, and there are two factors of safety of paramount importance: (1) employment of surgical asepsis and antisepsis in the care of the catheter in both the preoperative and postoperative periods and (2) employment of the intra-urethral method of digital enucleation of the prostate gland. The details of the operation and the special instruments used are described.

Between 1927 and 1932, Harris performed 371 prostatectomies by his plastic method. An operation in one stage was performed in 364 cases, and a two-stage operation in 49. In 356 cases the bladder was closed, and in 15 there was suprapubic drainage. There were 10 deaths, a mortality rate of 2.7 per cent.

Goldstein and Abeshouse<sup>38</sup> reported a case of infection by gas bacilli following perineal prostatectomy. In this case the development of the infection is undetermined. The following sequence of events offers a possible and probable explanation: *Clostridium Welchii*, which undoubtedly was present in the rectal contents before operation and was isolated from the rectal contents after operation, had spread through the rectovesical and rectoprostatic tissues following the operation and had resulted in an infection of the prostatic bed. The serosanguineous discharge from the operative wound had spread and contaminated the cutaneous surface of the right thigh, and the organism was carried in and implanted in the tissue of the right thigh as a result of hypodermic injections of digalen-Roche (Cloetta).

Familiarity with the clinical symptoms of infection by gas bacilli is essential and imperative in order to recognize and treat this complication successfully. The best results are dependent on early recognition of the disease and on the institution of immediate and thorough treatment. The treatment should consist of wide incision and drainage of the involved areas, including the operative wound, combined with serotherapy. A polyvalent serum injected intramuscularly and intravenously has yielded the best results.

38. Goldstein, A. E., and Abeshouse, B. S.: Gas Bacillus Infections in Urology, *J. Urol.* 31:547 (April) 1934.

*Resection.*—Caulk and Harris<sup>39</sup> stated that when the various high frequency cutting instruments are used, injury to tissue is often produced more deeply than is generally desirable and that it is often to some extent unavoidable. High current densities applied for more than a second may do injury at depths from a few millimeters to more than a centimeter. In order that tissue may be cut with high frequency currents intense heat is required at the active electrode. To produce this heat it is necessary for the current to pass through the tissue from an indifferent electrode and focalize at this point. In so doing, the paths of current, in their concentration toward the active electrode, generate varying degrees of temperature deep within the tissue, away from the point of active burning; in removal with the actual cautery approximately the same temperature is applied at the surface of the wound, but heat is not produced within the tissue, except by conduction from the surface.

The analysis of Caulk and Harris' experiments with high frequency currents shows conclusively that, at depths within the tissue of at least 1 cm. away from the active point of burning, changes in temperature well beyond the thermal death point of tissue have been produced, whereas with the actual cautery, heat registrations less than 0.5 cm. away, after repeated applications at the same site, have been negligible. The temperature which causes thermal death of tissue cells certainly lies between 44 and 52 C., probably at about 47 C.

An analysis of specimens removed by high frequency excision reveals varying grades of tissue destruction in these distant areas and, according to physical principles, demonstrates more pathologic insult than is noted in the tissue removed by the active electrode, for the simple reason that the current penetration in the underlying tissues is greater than that in the tissue removed. In removal with cautery the opposite is true.

Owing to the inherent quality of electric currents to produce heat in tissue and to the fact that these currents exert a deleterious effect on the tissue well away from the site of burning, it is essential that surgeons who are employing them should recognize their inherent dangers and exercise every precaution in modeling their technic. Bearing these points in mind, it is absolutely necessary in resection of the prostate gland to shift the scene of activity from one portion of the gland to another, in order to deviate the paths of current, avoid accumulative heating and not concentrate on any one segment except for a short time. It is also highly important that the minimal cutting current be applied for

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39. Caulk, J. R., and Harris, Wilbur: A Study of Comparative Effects of Various High Frequency Currents and of Thermal Cauterization in Prostatic Resection, *Tr. Am. A. Genito-Urin. Surgeons* 26:168, 1933.

the shortest possible time. If bleeding should occur it should be controlled with coagulating currents, which are far less penetrating and injurious. Removal of prostatic obstruction by cautery, or by methods which involve mild coagulation followed by excision of tissue or by cold cutting procedures followed by coagulation, unquestionably appears to have less inherent dangers than methods which employ any type of high frequency cutting.

#### URETHRA

*Urethrotomy.*—Barney<sup>40</sup> reported a simple method of performing external perineal urethrotomy which he has used successfully over a period of fifteen years. A soft rubber catheter is passed through the urethra into the bladder in the usual manner until its distal or outer end is almost level with the external meatus or with the orifice of the urethra. That end of the catheter is then grasped with a small clamp, preferably with a half-curved shank. The catheter and clamp are then passed on into the urethra until the point of the clamp can be felt pressing against the floor of the bulb. In the meantime, the free portion of the catheter has passed on into the bladder. The point of the clamp is now made to impinge against the perineum, bulging it sharply outward in the median line. An incision from 1 to 2 cm. in length is then made through the median raphe, the tissues being divided until the point of the clamp, the catheter still in its grasp, is exposed and worked through the incision. The end of the catheter is then firmly held with the fingers or by another clamp, the first clamp being opened and withdrawn backward from the urethra, leaving the catheter emerging from the perineal incision. The catheter is then drawn out until its eye occupies a suitable position within the bladder for uninterrupted drainage. Two transverse sutures are taken, one above and the other below the catheter, each being tied around it. These sutures should be passed quite deeply so as to include the corpus spongiosum, thus not only controlling whatever bleeding there may be, but also anchoring the catheter firmly in place. Care should be taken that while being passed through the urethra the clamp is not permitted to open and release the end of the catheter.

*Formation of Valve.*—Lowsley and Kirwin<sup>41</sup> stated that Young and his co-workers distinguished three general types of valve formation causing obstruction of the urethra, a classification which has been used by later writers on the same subject. In type 1 there is a ridge on the

40. Barney, J. D.: A Simple Method of Performing External Perineal Urethrotomy, *Surg., Gynec. & Obst.* 59:100 (July) 1934.

41. Lowsley, O. S., and Kirwin, T. J.: A Clinical and Pathological Study of Congenital Obstruction of the Urethra: Report of Four Cases, *J. Urol.* 31:497 (April) 1934.



floor of the posterior urethra, commencing at the verumontanum and continuing as a part of this structure. This ridge runs anteriorly to the bulbomembranous juncture where it divides into two processes, which are attached, in the form of a thin membrane, to the circumference of the urethra, at times completely encircling it. In type 2 there are similar membranous sheets, attached posteriorly to the verumontanum, in the region of the internal sphincter. In type 3 the membranes are without any relation to the verumontanum; these may be found in any portion of the posterior urethra. This type is called the "iris valve" because the valve resembles the iris of the eye. The membranous structure fills the entire circumference of the urethral lumen, but there is a small opening in its center; at times this is very minute or of such dimensions as to give the appearance of two folds lying at either side. The concave aspect of this form of membranous obstruction is always toward the bladder.

The symptoms of this lesion are manifested by the immediate effects of obstruction to the outflow of urine and by the more remote consequences of back pressure and urinary retention. The symptoms may be only those of secondary infection, the general condition resembling that seen in hypertrophy of the prostate gland. The most common symptom is a small urinary stream of diminished force, with straining and difficulty. The distended bladder is often palpable as high as the symphysis. Overflow incontinence, with a history of urinary difficulty or a previous diagnosis of enuresis, is likely to be the characteristic finding. In the advanced cases more distinct effects of the chronic obstruction to vesical drainage are observed. The clinical picture may simulate that of chronic diffuse nephritis or it may suggest the syndrome accompanying bilateral polycystic kidneys. In general, the symptoms are those of long-continued retention of urine and of infection.

There is a divergence of opinion as to the best method of eliminating these obstructions, although there is complete agreement as to the necessity of their immediate and entire removal. The condition is closely analogous to retention in hypertrophy of the prostate gland among men of middle age. Proper preliminary treatment of this condition among children is as important as suitable operative measures. In the first cases recognized attempts were sometimes made to dilate the obstruction forcibly with sounds, or the urethrotome was frequently used. In a few of his earlier cases Young performed operation intra-urethrally, using the punch instrument. Randall successfully employed fulguration in 2 cases. Hinman and Kutzmann followed several different plans of treatment in their 6 cases, among others, suprapubic cystotomy and perineal prostatectomy, with destruction of valves in the posterior urethra, or suprapubic cystotomy with splitting of the urethral folds.

A man aged 57 and an infant aged 2 years both presented median bars which were resected suprapubically; in other cases fulguration was used.

*Tumor.*—Lazarus<sup>42</sup> stated that carcinoma of the urethra is relatively rare. Any long-standing stricture of the urethra that does not yield to the usual methods of dilation and that is accompanied by a hemorrhagic urethral discharge should be thoroughly investigated. A stricture involving the membranous portion of the urethra, accompanied by a periurethral abscess which fails to respond to the usual methods of treatment, is also indicative of the possibility of carcinoma. A stricture of the urethra accompanied by a region of induration within the urethra, especially when accompanied by inguinal lymphadenopathy, suggests carcinoma, and biopsy should be made on a node removed from the groin. The treatment of choice is radical amputation of the penis, with block dissection of the inguinal and crural lymph nodes, followed by radiotherapy. The prognosis in cases of carcinoma of the urethra is poor, principally because of failure to make an early diagnosis.

#### TESTES

*Undescended.*—In 1926, Burdick and Coley<sup>43</sup> reviewed the operations for undescended testes at the New York Society for the Relief of the Ruptured and Crippled and were so discouraged with their end-results that they sought some better method of operating. Torek's results by orchiopexy, bringing the testis out through an incision in the scrotum, anchoring it to the fascia of the thigh and suturing the margins of the scrotal wound with those of the thigh, were so satisfactory that Burdick and Coley tried his method. They tried it first in selected cases, and they were so pleased with the results that they have adopted it as a routine procedure during the past five years at the New York Society for the Relief of the Ruptured and Crippled, in the children's surgical service of Bellevue Hospital and at the Lincoln Hospital. Burdick and Coley believe that the most suitable age for operation is between 8 and 12 years. This gives the testis a good chance to descend voluntarily if it will; it is larger and easier to manipulate, and the structures are more easily identified than among younger patients. Also, the organ has been placed in its normal position before the changes occur which come with puberty.

Burdick and Coley believed that if the undescended or maldescended testis is accompanied by a large hernia, an earlier operation is imperative, as, naturally, retention of the hernia by a truss is certain to exert pressure on an already underdeveloped organ and also prevents any tendency

42. Lazarus, J. A.: Primary Carcinoma of the Male Urethra, *J. Urol.* **31**: 823 (June) 1934.

43. Burdick, C. G., and Coley, B. L.: Undescended Testicle, *Ann. Surg.* **98**: 495 (Oct.) 1933.

to normal descent. Moreover, the continued trauma of a truss may, theoretically at least, predispose to malignant change in the undescended testis which, statistics have shown, is more prone to such degeneration than a normally situated testis. Trusses, therefore, are contraindicated. In cases of maldescent, especially when the testis is directed into the thigh instead of the scrotum, Burdick and Coley usually advised operation earlier, as further descent does not aid the testis in reaching the scrotum.

Torek's operation is described in detail; it consists principally of freeing the testis, lengthening the spermatic cord and then anchoring the testis to the thigh. This anchor is released at a second operation, when the scrotum has been sufficiently lengthened. In reviewing their operations by the Torek method Burdick and Coley were impressed by the fact that many times a testis which was only half or two-thirds normal size at the first operation had developed, and, at the second stage, approximated normal size. Other testes that had not been normal at this stage had continued to develop in the scrotum, and a follow-up note a year later elicited the information that the testis operated on was the same size as its fellow. Not infrequently it is difficult to palpate a testis buried in the thigh, and its actual size cannot be appreciated. In several instances in which Burdick and Coley thought that the testis was greatly atrophied they were surprised to find, after dissecting the organ from its bed in the thigh, that it had developed to normal proportions.

Burdick and Coley stated that they have completed 137 cases for final analysis; in 123, the results were excellent. The testis was normal in size and was lying free in the bottom of the scrotum. The scars in the region of the groin and thigh were the only evidences of a previously undescended testis. Their failures were due to technical errors; sufficient care was not used in dividing all the fascial bands, or the vessels were not sufficiently mobilized to permit the testis to be sutured to the thigh without tension. In a few cases the scrotum was sutured to the thigh in a position which caused too much tension on the suture line, so that the scrotum became partly or completely separated from the thigh. Five testes sloughed; 2 of these were sutured to the thigh without tension, but the suture line became infected, and the scrotum separated completely from the thigh. This separation, added to the infection, undoubtedly caused the sloughing. The other 3 were sutured to the thigh under too much tension. Nine were reported to be atrophic, and in 3 there was complete atrophy. One patient was discharged with a testis almost normal in size, but a follow-up note received one year later stated that the testis had atrophied and could not be palpated.

Burdick and Coley concluded that failures by Torek's method of orchiopexy can usually be attributed to some technical error. In their hands, so far, the end-results have been superior to those which they obtained by the former methods; they therefore do not feel justified in using any other type of operation.

Coley<sup>44</sup> stated that among 80,736 cases of inguinal hernia in males observed at the New York Society for the Relief of the Ruptured and Crippled, he found 1,357, or 1.65 per cent, in which the condition was associated with undescended or maldescended testes. From 1890 to 1918 operation had been performed in 4,453 cases of inguinal hernia of the male and in 334, or 7.5 per cent, of these cases the condition was associated with undescended testes. In the majority of these cases the condition occurred in children less than 14 years of age, inasmuch as in the earlier days adult patients with hernia were not admitted to the hospital. Of the 1,040 cases of hernia in adults in which operation was performed at the Memorial Hospital for the Treatment of Cancer and Allied Diseases by William A. Downes and by Coley, 49, or 4.71 per cent, were associated with undescended testis. The method of operation adopted by W. T. Bull and by Coley in 1892 and 1893 was, practically, the Bassini operation. However, they omitted the step of transplanting the cord, thus adding  $\frac{1}{2}$  inch (1.2 cm.) or more to its length. In addition, the cord was freed as high up as possible, and the bands of fascia, which usually made it possible to place the testis in the bottom of the scrotum, were divided. At about the same time, and quite independently, Bevan developed his operation for the undescended testis, which embodied the principles just described and had several additional features that were improvements over the method of Bull and Coley. One of these was purse-string sutures of the tissues just outside the external ring which prevented the testis from retracting into the canal or above the external oblique muscle. The second feature of Bevan's operation was the removal of a part or almost all of the veins of the cord. This naturally added to the length of the cord and to the possibility of placing it at the bottom of the scrotum without much tension. Bevan himself restricted excision of the veins to very difficult cases, and he did not use it as a routine operation.

In 1908 Coley reported his end-results of operation in 126 cases of undescended testis. Ten years later he reported 365 cases of undescended testis in which operation was performed by Downes and himself at other hospitals, making a total of 415 cases. Twenty-seven were of inguinoperineal type and 8 of inguinoperineal type; 149 patients were traced from one to twenty years after operation. While the results were, in their opinion, reasonably satisfactory; they were not ideal, since in a considerable number of cases the testis retracted

44. In discussion on Burdick and Coley.<sup>43</sup>

to the region of the external ring. There was no case of death or of recurrence of the hernia in the entire series. In reviewing the entire question, it seemed to Coley that it might be better to admit that the results obtained by the Torek operation are more satisfactory than those obtained by the older methods. At the same time he advised reserving the Torek method for the group of more difficult cases in which it is almost impossible to place the testis in the bottom of the scrotum without great tension and advocated that in the larger group of less difficult cases the Bevan operation, which has proved so highly satisfactory, be used.

There is still some difference of opinion as to the proper age for operating. Many years ago, Coley adopted the plan of waiting until the patient had reached the age of 10 or 12 years, unless there was some special reason for earlier operation, such as hernia which was not easily controlled. He still follows this plan, although some surgeons advise operating on patients as young as from 5 to 6 years. Coley's principal objection to the earlier operation is based on the fact that, in a considerable number of cases, the testis has descended of its own accord as the child has approached puberty. Some surgeons advocate removal of the undescended testis on the ground that it is of no special value. Although most writers regard it of no functional value there is no question but that the interstitial elements of the testis have an important bearing on the development of the male characteristics of the child, and for that reason Coley believes that the testis should not be removed. It is by no means true that the undescended testis is always functionless. He had 2 patients with bilateral undescended testes who married and had children.

Bevan<sup>44</sup> stated that the purpose of operations for undescended testis is to accomplish in the period required to perform the operation, possibly in an hour, what nature does slowly and gradually in the normal descent of the testis in a period of weeks and months. Many men who have undertaken these operations have not had a complete conception of the anatomy or of the technic required to perform the operation successfully. It is absolutely essential that the operator should know that when freeing the testis it is necessary to remove completely from the cord the structures which surround the testis and the cord, namely, the intercolumnar fascia, the cremasteric muscle fascia and the infundibuliform fascia, as well as to strip the cord completely of the vaginal process of peritoneum. Bevan has performed these operations in a large series of cases. He could not see any fair indication for complicating the operation of undescended testis with any scheme of suturing the testis to the thigh or of holding the testis down with traction sutures of any kind during the process of repair.

Before undertaking work of this kind the surgeon should know that there is a certain proportion of cases, possibly 10 per cent, in which the organs are so poorly developed, the structures of the cord so short, or the testis so far up in the abdominal cavity, that it is impossible to bring the testis down and place it in its normal position by any method of operation. Some of these rudimentary testes are best removed. Occasionally, when the cord is very short and the testis otherwise fairly normal, it may become necessary to divide the spermatic vessels in order to lengthen the cord sufficiently to place the testis in its normal position in the scrotum. Bevan seldom divided the vessels, and yet undoubtedly, in a limited number of cases, it is better to do this than to drop the testis back into the abdominal cavity or to remove it, because in a fair proportion of cases in which operation was performed in early life, even though the vessels are divided, the blood supply is sufficient to carry on the nutrition of the organ. If these testes are operated on when the patients are 5 or 6 years of age, which is probably the most favorable age, the operation can be performed very easily; most of the testes can be brought well down. The time to operate in these cases is early, long before puberty. It does not do any good to operate after puberty except for the psychic effect and for the cure of associated hernia.

Torek<sup>44</sup> stated that it was quite natural that every surgeon should select the technic that appealed to him and the one he was most accustomed to employ. In regard to attachment of the scrotum to the thigh by a subcuticular continuous suture, Torek has always used the interrupted suture through skin and subcutaneous tissue, and he tries to obtain broad apposition of raw tissue; this is done by taking very little skin and a good deal of raw tissue in adapting the parts. He considered that in this operation just as in any operation, especially in plastic surgery, it is important to obtain a very accurate apposition which leads to the most prompt and certain healing. Consequently, he has continued to use suture through the skin and subcutaneous tissue, and he has had no reason for deviating from this method of suture because, in his case, the scrotum has always remained attached. With the other method there were 2 cases in which it became loosened. Another point, not technical but fundamental, is the attachment of the testis to the fascia of the thigh, not by interposition of any other structure, but by direct attachment. The reason he considered this to be of fundamental importance is that, at least in the difficult cases, surgeons have to deal with a rudimentary testis or with a very poorly developed one. These badly developed testes usually have very small and short vessels, so that probably they are not well nourished from their own vessels, and attachment to the thigh gives the testis a new supply of blood. It is possible

that addition of this supply from a new source has something to do with the fact that in all their cases the testes have increased in size.

The matter of bringing both sides down at the same time has been mentioned. Torek admitted that there may be some cases in which this procedure is possible. However, he did not think that when surgeons have to deal with an absolutely rudimentary scrotum it would occur to them to try that method, because there is not enough skin to go across from one side to the other.

Lyle<sup>44</sup> called attention to the fact that the pull to which the testis is subjected in the Torek operation seems to have a stimulating effect on the opposite testis. He cited one of his cases of bilateral undescended testis in which, during the first stage of the Torek operation, the opposite testis descended into the scrotum. Since then he has observed this phenomenon in 2 additional cases. Regarding the applicability of this operation to the abdominal testis, one of his assistants has successfully transplanted such a testis to the bottom of the scrotum in three stages. In the first stage the testis was brought to the pubis, in the second to the thigh, and in the third stage, to the bottom of the scrotum. In this position the testis had developed and appeared to be normal.

Eggers<sup>44</sup> stated that other methods of traction have the disadvantage of leaving a canal at the bottom of the scrotum through which infection may enter. In children that is an important point. Torek's method is a closed one; it is strictly surgical, and it is a very delicate operation. In children great care has to be taken in handling the organ; the surgeon must not be rough, and if this caution is observed the results are excellent.

Eggers has performed the operation thirty times, and in all the cases the results were very satisfactory. There is a well developed pendulous scrotum, and the testis is situated at the lower part of the scrotum. In cases of bilateral undescended testes he always performs the operation in two stages because it has to be done carefully and it takes time, frequently as long as an hour and a half. There must be no undue tension on either the scrotum or the testis, and this is best accomplished by operating on one side at a time. The organs have a better chance to accommodate. At the first operation one testis is brought down; the next operation is performed about six months later, when the first side is separated and the other side is brought down. The third operation consists simply of separating the second side. There is no definite period which should be allowed between operations. Eggers has found that six months is sufficient time to allow the organs to accommodate themselves to their new position. Retraction of a testis has never occurred.

Gibbon<sup>44</sup> emphasized two points which he considered of primary importance irrespective of the type of operation performed: 1. The

necessity of freeing the component parts of the cord from surrounding tissues and from one another, which is the only way in which the testis can be brought down without tension. Mere cross-section of the sac and high removal of the proximal portion is but the first step in the mobilization. 2. Preservation of the blood vessels, even the veins, because in applying ligatures the tiny but essential arteries may be included. On this point depend the future position and development of the testis.

In his treatment of undescended testis Starr<sup>45</sup> frees the cord and sutures the tunica of the testis to it with a silver wire. Then after the scrotum has been stretched, the testis is placed in the bottom of the scrotum. The two wires are brought out of a nick at the bottom of the scrotum, and each is turned transversely; two horsehair stitches catch it there, and a loop at the other end is then sutured by fine catgut to the periosteum in the os pubis. His results have been unusually good.

*Testicular Function.*—Lower<sup>45</sup> stated that the fact that structure and function of the prostate gland are dependent on the endocrine activity of the testes is well known. Following castration the prostate gland becomes atrophic. Moore and his collaborators have demonstrated that the hormone extracted from the testis maintains the prostate gland in an apparently normal condition following castration. A series of experiments performed by Lower indicated that preparations of the male sex hormone will prevent atrophy of the prostate gland and seminal vesicles in castrated rats. In the complete absence of the hypophysis preparations of the male sex hormone will prevent regressive changes in the prostate gland and seminal vesicles and also in the testes. Experiments with parabiotic animals indicated that the hyperactivity of the pituitary gland occurring in the castrated partner may be modified by injections of testicular mush.

#### EPIDIDYMIS

*Infection.*—Buckingham,<sup>46</sup> in discussing nonspecific metastatic epididymitis, stated that bacteria may enter the blood stream from any focus during the course of infectious disease and may lodge in tissue and set up a reaction there. The end-result in any given case depends on the number of bacteria set free, the virulence, the susceptibility of the host and the specific localizing tissue. Because of its close embryologic relationship to the kidneys the epididymis tends to localize bacteria. Direct trauma plays an important part in the localization in the epididymis. The condition is seen most often during the course of respiratory infections. Any swelling of the epididymis without evidence of involvement of the

45. Lower, W. E.: The Exocrine and Endocrine Functions of the Testes. *J. Urol.* 31:391 (March) 1934.

46. Buckingham, W. W.: Non-Specific Metastatic Epididymitis, *J. Urol.* 31: 87 (Jan.) 1934.



genito-urinary tract indicates that infection has occurred by a metastatic route; thus a specific focus should be looked for and treated. After thirty-six hours of expectant treatment without benefit, incision and drainage should be performed in the acute cases and epididymectomy in cases of the pseudotuberculous type.

#### SCROTUM

*Filariasis.*—Young<sup>47</sup> reported 5 cases of filariasis of the scrotum and groin, 4 of which are quite alike. One, an ordinary case of chronic epididymitis following cystoscopy, is presented as a contrast to the other 4 cases. The patient in this case came from the same locality in Colombia, South America, as the others, but he presented entirely different lesions. The first 3 cases and the fifth, which are cited in detail, are remarkable in that the disease did not start in the testis, epididymis, vas deferens or vessels of the cord, but as a peritesticular or periepididymal disease. It was characterized by the ultimate formation of a dense mass of tissue, which in 2 cases had completely enveloped and compressed the epididymis without involving its tissues.

From its point of onset in the coverings of the epididymis or testis the disease has always traveled upward outside the spermatic cord. The filariae and surrounding inflammatory tissue become more or less loosely attached to the external fascia of the cord, in some instances forming large, globular masses, and in others, very fine lines suggesting lymphatic structures with small, beadlike enlargements along the course of the lymphatics. The presence of enlarged inguinal glands has been noted.

In none of the tissues removed has Young been able to find evidence of any ordinary bacterial inflammation, of tuberculosis, syphilis or malignant disease. The pathologic process was characterized particularly by the deposit or growth of large numbers of round cells, which ultimately had gone on to the formation of a marked fibrous sheath or covering. In some instances the tunica vaginalis was extensively involved, with adhesions to the testis, but the testis itself was free from disease, although in 1 case it was compressed and distorted by the fibrous tissue. The intrascrotal cord produced by the disease was characterized also by the presence of much vascularity, and around the walls of the blood vessels were numerous areas of round cell infiltration. These spaces might have been lymphatic channels, although in stained sections they were not seen to contain material, and nothing suggesting a large or small worm, larva or detritus resulting from the presence of a dead worm had been found. Nevertheless, it seemed evident that the disease was of filarial origin.

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47. Young, H. H.: Some Unusual Cases of Filariasis of the Scrotum and Groin, Tr. Am. A. Genito-Urin. Surgeons 26:120, 1933.

In the first case the numerous enlarged glands in various parts of the body of a man who had no evidence of syphilis were suggestive of filariasis, and in the second case, the presence of filariae in several members of the family, going back a generation or more, was presumptive evidence that this disease was the etiologic factor. Young stated that the condition may possibly be due to some process that has not been described before; he based his statement on the facts that nowhere in the literature had he been able to find exactly the same conditions he found in these cases and that filariae were not discovered.

Young believed that the disease is due to filariae, and that *Onchocerca volvulus* is probably the causative factor. His experience reveals that a radical operation should be performed in these cases, as the results he obtained have been very satisfactory.

#### VAGINAL STONE

Masson and Appell<sup>48</sup> stated that calculus of the vagina is a rare condition, only 20 cases having been described in the literature; to these they added 2 more. This condition occasionally develops in association with vesicovaginal fistula, foreign bodies, stagnation of urine due to paraplegia and enuresis, calcified fibroid tumors which had migrated into the vagina and vaginal cysts. In some cases the cause was unknown. The stones were all composed of urinary salts, except those which were due to calcified fibroid tumors.

The symptoms are urinary incontinence, pelvic and perineal pain and fetid vaginal discharge with occasional bleeding and dyspareunia. The stone is usually felt in the vagina and is easily removed digitally, except in rare cases in which the vaginal orifice is contracted or completely closed. In such cases some type of operation on the vaginal outlet is necessary. Removal of the stone and repair of the fistula, followed by irrigations of the bladder and vagina when indicated, usually give complete relief.

#### URINARY INFECTIONS

Band, Dunlop and Dick<sup>49</sup> reported the results of their studies of infection of the urinary tract from the pathologic, therapeutic and bacteriologic standpoints. Band demonstrated the pathologic changes in the various types and stages of infections: acute pyelonephritis with resolution and with suppuration, paths of intraparenchymatous reinfection, chronic pyelonephritis with suppuration and with fibrous tissue replacement of tubules and glomeruli and atony and dilatation of the pelvis and calices, and pyonephrosis. These are best illustrated by

48. Masson, J. C., and Appell, A. A.: Vaginal Calculi, *West. J. Surg.* **42**: 132 (March) 1934.

49. Band, David; Dunlop, D. M., and Dick, I. L.: Studies in Urinary Infection. Pathological, Therapeutic and Bacteriological, *Edinburgh M. J.* **40**:65 (May) 1933.

"whole sections" of the kidney. Focal infection throughout the body may be followed by metastasis to the urinary tract. In 77 per cent of Band, Dunlop and Dick's cases the infecting organism was *Bacillus coli*, and the large intestine was the principal source of infection.

In a consideration of the descending infections it has been noted that, prior to their onset, there have been signs and symptoms of alimentary disturbance with evidence of renal irritation, albuminuria and an excess of oxalates, urates or phosphates, indicating a metabolic disturbance. It is suggested that the kidney is injured by a bacterial or chemical toxin prior to the onset of infection. This has been confirmed by experiments which show that, after inoculation of the blood stream with *B. coli*, pyelonephritis is not easily produced unless the kidney has been injured previously by a bacterial or chemical toxin.

Ascending infections from the lower part of the urinary tract have been shown to occur through the wall of the ureter in the periureteral lymphatic structures. It is doubtful whether ascending infections ever progress through the lumen of the ureter when the ureteral orifices are competent.

Several factors contribute to the pyelonephritis of pregnancy. Pelvic and ureteral atony and dilatation from changes in the circulation and innervation of the pelvic viscera, including the pelvic portion of the ureter, may occur. The unknown toxins of pregnancy, which in addition, produce renal irritation contribute to the condition. This combination makes the kidney a fertile field for blood-borne infection during pregnancy.

The care of infections in the urinary tract is modified by the contributing lesions and the stage and type of the infection. Chief interest lies in notoriously resistant, subacute, chronic and recurring pyelonephritis and cystitis. This stage has been arrived at as a result of : (1) the existence of a source of reinfection outside the urinary tract, (2) the presence of stasis within the urinary tract, which permits the organism to multiply and adapt itself to conditions there and (3) residual infection in the renal parenchyma, which has been recognized as a localized area of congestion and small cell accumulation surrounding a disorganized tubule. Such an area tends to remain active and unhealed while the circulation and drainage of the renal parenchyma are deficient.

Particular attention should be paid to the alimentary tract as a source of infection in the care of infections of the urinary tract as a whole. In the direct attack on the urinary tract the object should be: (1) to encourage and aid drainage of the renal pelvis and (2) to increase the bactericidal qualities of the urine. The first is best accomplished by repeated pelvic lavage. The second is obtained by lowering the  $p_H$  of the urine by the ketogenic diet, using the ammonium salts and causing

diuresis by the ingestion of large quantities of water, so that the output of urine reaches 3,000 cc. in twenty-four hours.

One hundred and thirty-six cases of pyelocystitis are analyzed as to the nature of the infection, sex incidence, average duration of symptoms and end-results. Twenty-three patients, or 17 per cent, were unimproved by the ordinary methods of treatment, and this "intractable" group were hospitalized and put on the ketogenic diet without other treatment. The management of, and the results obtained in, this group are analyzed by Dunlop. He concluded that ketonuria has strong bactericidal powers and that in the future this diet may be used in the treatment of intractable, chronic pyelocystitis. He also emphasized the drawbacks. It requires hospitalization, close clinical control of the patient and a competent dietitian. Not all patients can take the diet, and it is not invariably successful, although it may be used when other methods have failed and may yield very successful results.

Following bacteriologic researches to measure the bactericidal properties of ketonuria and to determine whether these properties are due to changes caused by the diet in the reaction of the urine or to some unknown antiseptic substance, Dick concluded that: 1. Ketonuria has a bacteriostatic effect, at least for the type of organism used. 2. This effect is not entirely due to an increase in the acidity of the urine. 3. It is still sub judice whether a certain degree of acidity is essential for the production of this bacteriostatic effect. 4. Any evidence as to the nature of the active substance is, so far, only of a negative kind.

Campbell,<sup>50</sup> in discussing chronic pyuria of juveniles, stated that it usually indicates a potentially serious urologic disease. It is seldom due to uncomplicated infection in the urinary tract. The methods of diagnosis and treatment are identical for juveniles and for adults. The diagnosis can be made only by a careful, complete urologic examination. The treatment often requires radical surgical attack. By properly directed urologic treatment, a gratifying number of juvenile patients may be cured. A much larger number will be improved and the renal destruction greatly diminished or checked. Nearly all the others can be made more comfortable. Campbell is convinced that it is the duty of all urologists to bring these facts more forcibly to the attention of the medical advisers of the young.

McCarthy and Ritter<sup>51</sup> discussed 293 cases which were referred for bacteriophage therapy. Bacteriophage was obtained in 112 of these cases. Definite data were secured in 69 cases, of which 43 were excluded for the following reasons: It was found that results were

50. Campbell, M. F.: Chronic Pyuria in Juveniles, *J. Urol.* **31**:205 (Feb.) 1934.

51. McCarthy, J. F., and Ritter, J. S.: Bacteriophage in Genito-Urinary Tract Infections, *Tr. Am. A. Genito-Urin. Surgeons* **26**:123, 1933.

negative in 16 of the 69 cases; patients were resistant after treatment in 3; symptomatic improvement was present in 24 (not bacteria-free), and symptomatic and bacteriologic cures were obtained in 25, or more than 36 per cent of the cases.

Of 16 patients with staphylococcic septicemia, most of whom were cared for in other departments of the hospital, 6 have recovered following treatment with bacteriophage, which is most unusual in so grave a condition. McCarthy and Ritter stated, however, that in a certain percentage of cases of apparent cure later cultures of the same or of other bacteria have been developed.

#### HEMATURIA

Debenham<sup>52</sup> has analyzed 742 consecutive cases of hematuria among patients in the genito-urinary department of the London Hospital from 1924 to 1930. He reported the findings under the following headings: (1) general consideration of the causes of hematuria, sex incidence, severity of the bleeding and common causes thereof; (2) consideration of the various conditions giving rise to hematuria and relative importance of evaluation of the main symptoms, and (3) consideration of the unexplained cases with results of the follow-up investigation.

Only patients with gross hematuria were included in the study. Each patient was subjected to the various steps of a complete urologic study, as indicated by the objective findings.

Cystoscopic examination is important during hemorrhage. From this study it was found that papilloma and carcinoma of the bladder are the most common causes of hematuria among men and that inflammatory conditions of the urinary tract are the most common causes of hematuria among women. When hematuria is a presenting symptom among men, there is a 50 per cent possibility that it is due to papilloma or carcinoma of the bladder. Among women the cause is as likely to be inflammation as neoplasm. With hematuria as the only symptom in 65 men, there was a two to one chance that the condition was due to papilloma or to carcinoma of the bladder. Among women (10 cases) the most common cause was renal calculus. In men over 50 years of age the prostate gland is a common cause of hematuria. In 130 cases of hematuria of men over 60, 43 per cent were suffering from papilloma or carcinoma of the bladder and 37 per cent from simple or malignant enlargement of the prostate gland. Carcinoma of the bladder is not infrequently associated with enlargement of the prostate gland; in some cases the symptoms are rather similar, and, unless cystoscopy is performed, the case may for a time be considered to be one of prostatic enlargement, and valuable time may thus be lost.

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52. Debenham, R. K.: An Investigation of Seven Hundred and Forty-Two Cases of Haematuria, *Brit. J. Surg.* 21:44 (July) 1933.

The common causes of hematuria in the different decades of life are given on a chart. The conclusion is that hematuria is rare in the first two decades of life. In the second and third decades inflammatory conditions and calculi are the most common causes in both sexes. Neoplasm becomes the most common cause of hematuria among men in the fifth decade and in both sexes in the sixth decade of life.

Carcinoma of the kidney is rare; it was the cause of only 2.5 per cent of all the cases of hematuria (men, 3 per cent, women, less than 0.5 per cent).

Renal calculi not uncommonly cause hematuria, which may be almost or quite painless.

The diagnosis of hematuria due to varicose vesical veins must be made with great caution, unless the bleeding is actually seen to be coming from a varix.

In the 66 cases of unexplained hematuria, 49 patients were traced and the after-history discovered, and in 4 (8 per cent) of these the patients reported that calculi had either been passed or removed. Thirty-three patients (67 per cent) were almost or quite well, further bleeding not having occurred. Eight patients (16 per cent) reported a recurrence of bleeding on one or more occasions. All were well or only slightly inconvenienced, except a man who had syphilis and who had become blind. Four patients (8 per cent) had died, 2 of acute pulmonary conditions not connected with the hematuria, 1 of carcinoma of the prostate gland eight years after his attendance at the hospital, and 1 of apoplexy.

The most difficult cases to diagnose are those in which there are few symptoms other than the hematuria which has ceased by the time the patient comes to the hospital. Cases of unexplained hematuria fall into several different categories; the prognosis is good if nothing abnormal can be found on full urologic investigation.

#### ANESTHESIA

Rovenstine<sup>53</sup> reported a study of spinal and transsacral anesthesia in cases of transurethral resection of the prostate gland, which is of value in further work for this surgical technic. Transurethral resection of the prostate gland is a major surgical procedure so far as anesthesia is concerned, and the same complications may be anticipated as those which occur when the gland is enucleated.

Spinal anesthesia, with procaine hydrochloride skilfully administered, is satisfactory. The complications which are generally recognized to contraindicate its use are involvement of the central nervous system,

53. Rovenstine, E. A.: Anesthesia for Transurethral Prostatic Resection. A Comparative Study of Transsacral and Spinal Blocks. *J. Urol.* **31**:633 (May) 1934.

turbidity of the spinal fluid, the presence of a lesion at the site of injection, a markedly diminished vital capacity or extreme variations from the normal blood pressure. Anesthesia with spinal block should not be permitted to affect intercostal activity. Advantage should be taken of methods to insure proper placing of the anesthetic solution in the lumbar region, namely, position of the patient, injection in the most caudal interspace accessible, slow rate of injection, an amount of diluent for procaine hydrochloride in the ratio of 1 cc. for each 100 mg. of the drug, and the important addition of dextrose to the solution of spinal fluid and procaine hydrochloride.

The amount of procaine hydrochloride used in this series of spinal block operations was excessive. Doses of from 50 to 75 mg. are sufficient for more than an hour of anesthesia if properly injected, and more than 100 mg. should never be required.

Transsacral block anesthesia with procaine hydrochloride and epinephrine gives satisfactory results. It requires skill on the part of the anesthetist and must be done completely in every case. The difficulties encountered are usually due to the wide variation of the sacrum in different persons. The shape and structure of the bone vary with individual characteristics of bodily build and from changes due to metabolic diseases. The total amount of solution needed depends on the time necessary for the operation. In this series too much was often used. In practically all cases a total of from 40 to 50 cc. of 1 per cent solution of procaine hydrochloride with epinephrine (1:1,000), 5 minims (0.3 cc.) per hundred cubic centimeters, properly placed, suffices for two hours of satisfactory anesthesia. Contraindications to transsacral block, namely, a lesion at the point of injection and idiosyncrasy to procaine hydrochloride, are fewer than with spinal block. In transsacral block it is imperative to delay the operation until the anesthetic agent has had at least twenty minutes to exert its action. Sacral nerves carry a layer of dura mater throughout their length through the sacral foramina, retarding the action of drugs and making for slow penetration. For this reason, and to allow the anesthetist an opportunity to observe the patient's reaction to procaine hydrochloride and epinephrine, the injection should be made slowly. Proper transsacral block cannot be accomplished in less than fifteen minutes, and more time should be allowed for safety.

Preliminary medication was overdone in this series. The administration of derivatives of barbituric acid preoperatively is advantageous as a prophylaxis to toxicity caused by procaine hydrochloride, but their use night and morning is hardly warranted. A barbiturate at night and morphine or morphine combined with atropine or scopolamine hydrobromide were unnecessary in this group. Patients of the average

age in this series have a metabolism curve near the base line, require less psychic sedation and are more susceptible to hypnotic and to sedative drugs than the average, active person. A short-acting derivative of barbituric acid such as pentobarbital-sodium in small doses,  $\frac{1}{2}$  grain (0.032 Gm.), given approximately thirty minutes before anesthesia is started suffices in most cases.

The anesthetic agents and the technic used in cases of transurethral resection of the prostate gland are not nearly so important in securing satisfactory results as are the keen judgment, technical skill and experience of the anesthetist.

Hess<sup>54</sup> stated that epidural anesthesia is ideal for operations on the kidney and upper part of the ureter when the general condition of the patient is such that other forms are contraindicated or dangerous. It should not be used as a routine procedure, however. In his experience there have been no postoperative complications from its use. A large percentage of the patients operated on complained of discomfort during the operation, but it is considered the safest of all procedures.

Foulds and Douglas<sup>55</sup> stated that the field of usefulness of spinal anesthesia increases in proportion to the familiarity with the method. The contraindications have diminished as experience with this type of anesthesia has been gained. Since ephedrine has been used as a routine the number of cases in which the fall in blood pressure has been alarming has been reduced to a minimum, and the contraindications to spinal anesthesia in hypotension have been removed. By selecting cases suitable for each drug the results have improved. Although procaine hydrochloride in doses up to 150 mg. is suitable for operations on the lower part of the urinary tract, untoward symptoms frequently follow the administration of larger doses for higher and longer anesthesia. Such anesthesia for renal operation can be more perfectly obtained with fewer unpleasant symptoms by the use of nupercaine in doses up to 20 cc. of a 1:1,500 solution. The postanesthetic sequelae have been negligible and the postoperative complications fewer than with general anesthesia. Spinal anesthesia is considered by Foulds and Douglas to be the best choice in the majority of operations on the genito-urinary tract.

Abeshouse<sup>56</sup> stated that, in a period of forty months at Sinai Hospital, spinal anesthesia was used in 327 operations on the genito-urinary tract. This series of operations included 27 resections of the prostate gland.

54. Hess, Elmer: Epidural Anesthesia in Urological Surgery, *J. Urol.* **31**:621 (May) 1934.

55. Foulds, G. S., and Douglas, H. S.: Spinal Anesthesia in Urology, *J. Urol.* **31**:607 (May) 1934.

56. Abeshouse, B. S.: In discussion on Foulds and Douglas,<sup>55</sup> p. 615.



Twenty-four patients died following operation, an average operative mortality of 7.3 per cent. Only 1 operative death could be attributed directly to the spinal anesthesia. In this case the anesthetic was administered during a suprapubic cystotomy and resection of a papilloma of the bladder of a man aged 46. On the third day after operation, signs of pneumococcic meningitis developed, and the patient died of meningitis and lobar pneumonia on the fifth day. The 24 cases in which death occurred in this series included those in which it occurred during the time of administration of the anesthetic or during the operation as well as those in which the patient survived the operation and did not die until some time later in his stay in the hospital.

A preliminary dermal injection of  $\frac{3}{4}$  grain (0.048 Gm.) of ephedrine and procaine hydrochloride was used. The drugs employed in this series included procaine hydrochloride, nupercaine, *p-n*-butylaminobenzoyl-*di*-methylamino- ethanol hydrochloride and a proprietary procaine preparation. In the majority of cases, particularly in those in which the time of operation did not exceed seventy-five minutes, from 100 to 150 mg. of procaine hydrochloride was used. In cases in which the operating time was expected to exceed seventy-five minutes, 200 mg. of nupercaine was used in the early cases. This drug was soon discarded in favor of 22 cc. (20 mg.) of *p-n*-butylaminobenzoyl-*di*-methylamino- ethanol hydrochloride because of the delirium which developed soon after anesthesia and which lasted from six to twelve hours in 3 of the cases. In Abeshouse's experience, spinal anesthesia has proved to be excellent for operations on the genito-urinary tract.

#### UROGRAPHY

Mertz and Hamer<sup>57</sup> stated that lateral pyelography is practical and can easily be performed on the ordinary x-ray cystoscopic table without added discomfort or risk to the patient. The renal pelvis and ureter can be satisfactorily visualized in the majority of cases. A study of the lateral pyelogram should include the vertical and anterior position of the kidney, the degree of horizontal and vertical rotation of the kidney, the outline of the pelvis as compared to that in the antero-posterior pyelogram and the course followed by the ureter. Mertz and Hamer stated that their cases have been too few to establish general rules of interpretation, but they believed that their experience was sufficient to justify bringing the subject to the attention of others.

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57. Mertz, H. O., and Hamer, H. G.: The Lateral Pyelogram: An Investigation of Its Value in Urologic Diagnosis, *J. Urol.* **31**:23 (Jan.) 1934.

THE FACTOR OF SPASM IN THE ETIOLOGY  
OF PEPTIC ULCERS

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Exalto<sup>1</sup> was the first investigator to develop a technic which regularly produced chronic ulcerations of the jejunum. He severed the stomach immediately above the pyloric valve according to the method of von Eiselsberg. The distal and proximal ends of the stomach were closed. The jejunum was severed distal to the duodenojejunal flexure, and both ends were closed. The distal jejunum was anastomosed to the stomach near its proximal closed end. The duodenum was anastomosed into the jejunum 20 cm. distal to the gastrojejunal anastomosis, according to the method of Roux, or into the colon (fig. 1). Exalto therefore deserves the credit for the originality in implanting the duodenum into the colon and thus completely diverting the alkaline duodenal contents from the gastrojejunal anastomosis.

Exalto performed a typical gastrojejunal anastomosis in seven dogs according to the method of von Eiselsberg without the short-circuiting operation of Roux. He failed to obtain ulcers in any of the animals.

In four dogs Exalto performed a typical von Eiselsberg exclusion anastomosis and diverted the duodenal contents about 20 cm. from the gastrojejunal anastomosis. He also fed his animals certain amounts of hydrochloric acid. In three of four animals he produced typical jejunal ulcers. In the last three dogs he performed a typical von Eiselsberg exclusion gastro-anastomosis and diverted the alkaline duodenal contents into the colon. He was able to produce typical ulcers of the jejunum in each animal operated on in this manner.

This was the first time that a method was found which produced jejunal ulcers in 100 per cent of the experiments (fig. 1). Unfortunately, Exalto's work does not seem to have been carefully read by investigators in this country. It is also to be regretted that Exalto's

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Assistance for these experiments was advanced by a gift of the General Education Board.

1. Exalto, J.: *Ulcus jejuni nach Gastroenterostomie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 23:13, 1911.

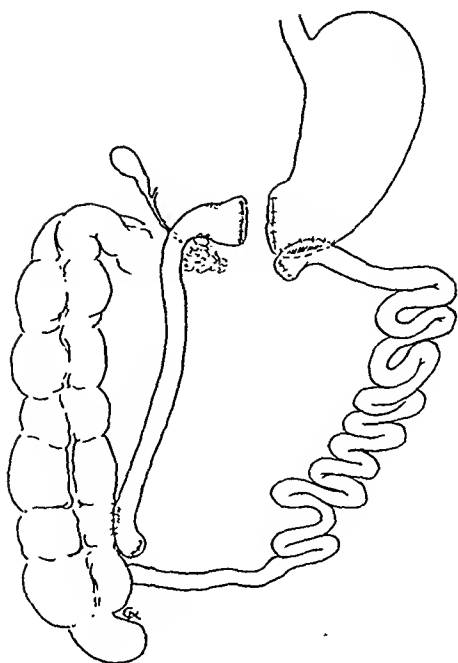


Fig. 1.—A diagram of the method elaborated by Exalto in 1911, which produces ulcers with regularity.

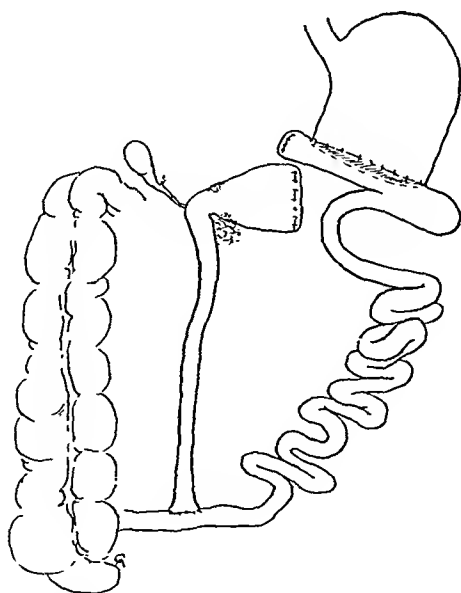


Fig. 2.—A Devine exclusion operation with an Exalto short-circuiting operation which regularly produces ulcers. An entero-anastomosis opposite the gastro-anastomosis releases the spasm and prevents the formation of ulcers.

findings have been erroneously quoted by some (McCann<sup>2</sup> and Matthews and Dragstedt<sup>3</sup>).

In the last few years interest in the etiology of peptic ulcer has been renewed, and many investigators have used the typical Exalto technic or some modification of it. Many have been able to corroborate Exalto's findings (Mann and Williamson,<sup>4</sup> Ivy,<sup>5</sup> Steinberg and Proffitt,<sup>6</sup> Matthews and Dragstedt<sup>3</sup> and others). Winkelbauer<sup>7</sup> repeated Exalto's experiments but divided the stomach in the middle, thus excluding the entire motor part. The duodenal contents were diverted into the lower ileum or the colon (fig. 2). He was able to produce ulcers in every dog operated on in this manner. Steinberg<sup>8</sup> used the same technic as Winkelbauer but diverted the duodenal contents 70 cm. away from the gastrojejunal anastomosis. Definite chronic ulcers of the jejunum developed in 75 per cent of his animals. Matthews and Dragstedt<sup>3</sup> have demonstrated that ulcers of the jejunum are produced under certain conditions with regularity only if the duodenal contents are diverted into the colon or are prevented from finding their way back into the stomach by valve formation. This would offer a probable explanation as to why Steinberg was able to find only 75 per cent of ulcers in his animals.

Winkelbauer has made an attempt to study the relation of the spastic condition of the jejunum anastomosed to the stomach to the genesis of postoperative peptic ulcers. He utilized the method of Kreidel, who demonstrated on dogs that circular and longitudinal muscle layers can be removed from large areas of the stomach and intestine without apparent harm to the dog. The mucosa left after the muscle layers have been stripped off is sufficient protection against perforation. This procedure is somewhat similar to the Weber-Rammstedt operation for hypertrophic stenosis of the pylorus in infants. Winkelbauer used Exalto's method of implantation of the duodenum in the lower part of

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2. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

3. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcers, *Surg., Gynec. & Obst.* **55**:265 (Sept.) 1932.

4. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409 (April) 1923.

5. Ivy, A. C.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and the Upper Intestine: Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcers, *Am. J. Surg.* **11**:531, 1931.

6. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, *Arch. Surg.* **25**:819 (Nov.) 1932.

7. Winkelbauer, A.: Studien ueber die Verhütung des Ulcus pepticum post-operativum im Experiment, *Arch. f. klin. Chir.* **143**:649, 1926.

8. Steinberg, M. E.: The Exclusion Operation for Duodenal Ulcers, *Am. J. Surg.* **23**:137 (Jan.) 1934.

the ileum or the large bowel, excluding the motor part of the stomach similar to that suggested by Devine for duodenal ulcer (fig. 2). Winkelbauer also stripped the longitudinal and circular muscles of the jejunum anastomosed to the stomach for a distance of from 15 to 25 cm. Only two of the dogs survived from thirty-four to seventy days. In none of the animals was an ulcer demonstrated. In our opinion these experiments did not prove anything conclusively, since a total of two negative findings may easily be considered as a mere coincidence. Nevertheless, we deemed the speculations of Winkelbauer of interest and importance, and extended and augmented his experiments in various ways.

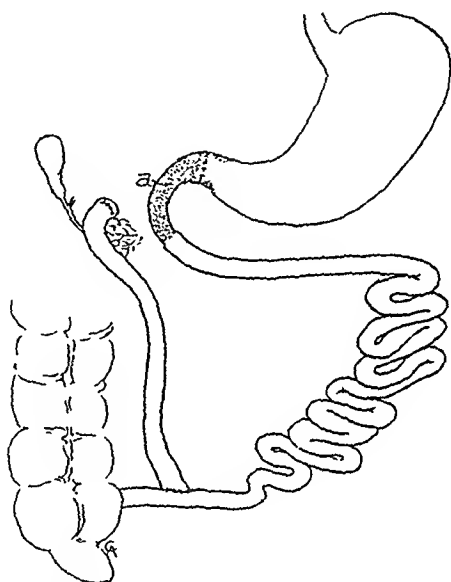


Fig. 3.—An Exalto short-circuiting operation and an end-to-end anastomosis between the pyloric valve and the jejunum. Ulcers formed regularly in from 90 to 100 per cent of the experiments. No ulcers were found where the muscle layer was stripped (a).

#### EXPERIMENTS

*Type 1.*—Numerous investigators have diverted the alkaline duodenal contents into the ileum or the cecum, according to the method of Exalto, and anastomosed the jejunum to the pyloric valve end-to-end. Acute or chronic ulcers occurred with regularity (Mann and Williamson,<sup>4</sup> Ivy,<sup>5</sup> Steinberg and Proffitt,<sup>6</sup> Matthews and Dragstedt<sup>3</sup> and others). Seven of our animals operated on according to the aforementioned method have survived from five to sixty-nine days, and acute or chronic ulcers of the jejunum developed in each. Using these seven animals as controls, we operated on another series of animals, diverting the duodenal contents into the ileum and anastomosing the pyloric valve to the jejunum, as in the control animals, but in addition we stripped the longitudinal and circular muscle of the jejunum for a distance of about 10 cm., beginning at the pyloric valve (fig. 3). By our method a narrow strip of muscle is left at the mesenteric border for the

preservation of the blood supply. Since the jejunum is anastomosed to the pyloric valve end-to-end, before the stripping takes place, a small circular part of the jejunal muscle is left intact near the pylorus. There also results a small triangular area of jejunum covered by muscle near the mesenteric border at the gastrojejunal anastomosis. The stripping of the muscle is easily performed by splitting the muscle wall longitudinally with a knife and then separating it with the finger covered with gauze or by cutting over a spread mosquito forceps which is introduced between the muscle layers and the submucosa. Apparently no harm results from this procedure; the hemorrhage is easily controlled by the application of hot, moist sponges. At postmortem examination hair mixed with débris was occasionally found in the loop stripped of its muscle. The omentum completely covered the jejunal area (fig. 5).

Of several animals operated on according to the aforementioned method, ten survived from seven to seventy-six days. Eight dogs were observed for a period

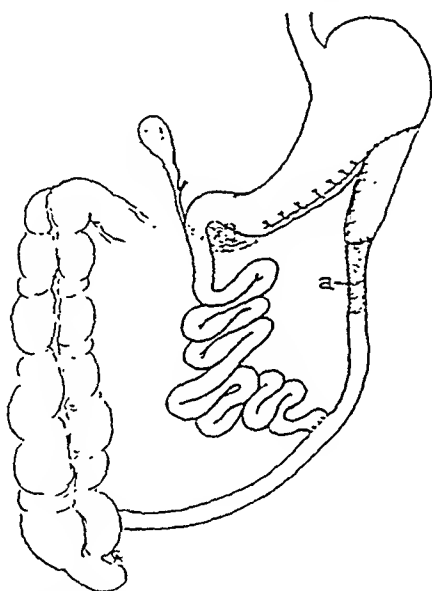


Fig. 4.—An anastomosis between a Pavlov stomach pouch and the ileum according to Matthews and Dragstedt. Ulcers formed in 100 per cent of the experiments. No ulcers occurred where the muscle was stripped (a).

of from twenty-one to seventy-six days. In the control experiments in which the muscle was not stripped, this type of experiment produced ulcers in 100 per cent of the animals in about the same period of observation. In none of the ten dogs in which the muscle of the jejunum was stripped did any ulcers develop in the area of the mucosa, where three fourths of the circumference of the longitudinal and circular muscles was stripped. In dog 145 there was a small chronic ulcer near the pyloric valve. The ulcer, however, was surrounded with a part of the jejunal wall, its muscle layers intact (fig. 5). A small chronic ulcer also developed in dog 152, in the jejunum near the pyloric valve. This ulcer was also surrounded by the jejunal wall, with its muscle layers intact. A large ulcer with a deep crater penetrating into the surrounding structures developed in dog 146 (fig. 4). This ulcer began at the mesenteric border where the muscle layers of the jejunum were intact and then penetrated into the neighboring mucosa where the muscle

layers were stripped. The most interesting observations in these experiments were the finding of acute and chronic ulcerations in the jejunum exactly where the muscle layer began its normal intact course, or about 10 cm. from the pyloric valve (figs. 5 and 7). This is, according to our knowledge, the first time that such an observation has been recorded. It was also interesting to notice that the lumen of the jejunum where the muscle wall was stripped was larger than the part of the jejunum where the muscle wall was intact (figs. 5, 6 and 7).

Dog 145 was observed for seventy-four days. We have already recorded the finding of a small chronic ulcer near the pyloric valve, but in addition there was a narrow ulcer about 15 cm. long, beginning exactly where the muscle layer began its normal intact course and therefore separated from the ulcer at the pylorus by a distance of 10 cm.

Dog 152 was observed for forty-eight days. In addition to a small ulcer near the pylorus, already recorded, there were two small chronic typical "kissing ulcers"

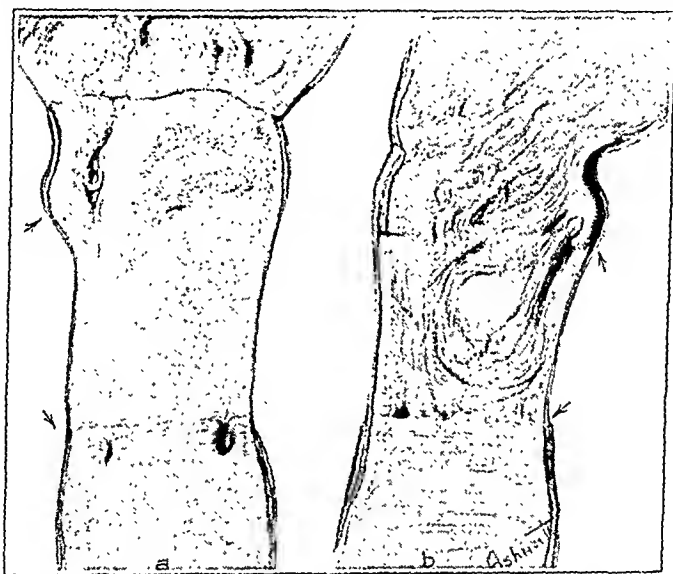


Fig. 5.—A gastro-anastomosis (a) between the stomach and the jejunum with an Exalto short-circuiting operation (fig. 3). The area between the arrows shows where the muscle layer was stripped from the jejunum. A small ulcer near the pyloric valve and two chronic "kissing ulcers" exactly where the muscle layer begins its intact course, or about 10 cm. from the pyloric valve, are seen. On the peritoneal surface (b) of the same specimen the omentum covers the area in which the muscle is stripped.

in the mucosa located exactly where the muscle layer began its intact course, and therefore likewise about 10 cm. distal to the pyloric valve (fig. 5).

Dogs 149 and 144 lived from seven to ten days. No ulcerations were found near the pylorus or in the mucosa of the jejunum where the muscle was stripped. On the other hand, in each of the dogs, at a distance of 10 cm. from the pylorus, exactly where the muscle began its intact course, there were acute defects. A narrow ulcer, 1 cm. in length, following a longitudinal course (dog 144, fig. 7) and a smaller one (dog 149) were found. None of the ten dogs observed from seven to seventy-six days had ulcerations in the area in which the muscle was stripped.

*Type 2.*—Winkelbauer formed a large Pavlov pouch and anastomosed various parts of the small intestine to the pouch. He was successful in producing an ulcer in the ileum. Matthews and Dragstedt have performed similar operations but also diverted the passage of the intestinal contents from the anastomosis between the pouch and the small intestine. Where the ileum was anastomosed to the



Fig. 6.—An anastomosis between the stomach and the jejunum, end-to-end with an Exalto short-circuiting operation (fig. 3). In this dog the ulcer occurred where there was still a little muscle left near the pyloric valve and penetrated into the jejunum which had been stripped of its muscle. This specimen shows the mechanical factor of the propelling peristaltic force of the stomach.

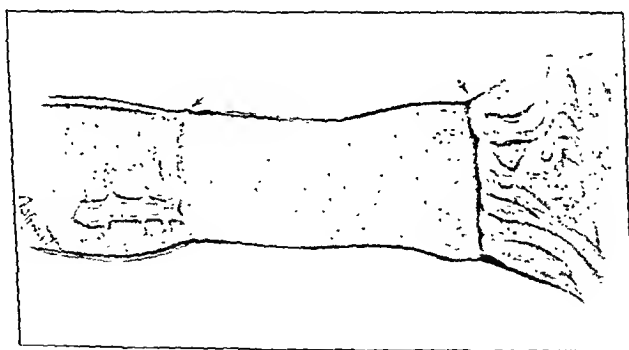


Fig. 7.—An end-to-end gastrojejunal anastomosis with an Exalto short-circuiting operation (fig. 3). The arrows point to the jejunum stripped of its muscle walls. A narrow superficial ulcer, covered by a diphtheritic membrane beginning exactly where the normal muscle layer starts its intact course, can be seen.

pouch, ulcers resulted in every animal operated on in this manner. We have used a technic described by Matthews and Dragstedt in several animals and in addition stripped the longitudinal and circular muscle layers of the ileum for a distance of 10 cm. distal to the anastomosis (fig. 4). Several animals were operated on



in this manner, but only six survived from eleven to one hundred and fifteen days. In none of the animals did an ulcer develop where the muscle was stripped. Dog 137 was found dead eleven days after the operation. The postmortem examination revealed two small superficial ulcerations in the ileum distal to the pouch where the longitudinal and circular muscle layers began their intact course. If we remember that Matthews and Dragstedt operated on six dogs in the same manner and found ulcers in each animal, our findings become interesting, since they compare well with the results of experiment type 1 recorded earlier, in which the muscle layers of the jejunum were stripped.

*Type 3.*—Again we wish to call attention to the fact that Winkelbauer operated on several dogs according to Exalto's short-circuiting technic, diverting the duodenal contents to the colon and excluding the motor part of the stomach, according to the method known in this country as that of Devine (fig. 2). Winkelbauer was able to observe ulcers in 100 per cent of these experiments. In twelve animals observed from nineteen to forty-three days, operated on by one of us (M. E. S.) according to the method described, large chronic ulcers formed in 75 per cent. These results were not as uniform as Winkelbauer's and can be explained by the fact that the alkaline duodenal contents were not diverted into the colon but somewhat higher into the small intestine. These twelve animals were used as control experiments. We then succeeded in keeping alive for from seventy-two to two hundred and twenty-five days four animals which were operated on in the manner already described. In addition, we performed an entero-anastomosis, according to the method of Finney, opposite the gastrojejunal anastomosis (fig. 2). Our object was to release the spasm of the jejunum at the gastro-anastomotic opening. None of these four dogs, observed for a long period of time, had ulcers. One of the control dogs operated on according to Exalto's short-circuiting method and Winkelbauer's and Devine's exclusion operation had a huge chronic, deep ulcer occupying the whole area of the jejunum anastomosed to the stomach. We formed an entero-anastomosis immediately distal to the ulcer. This dog was killed a month later; at that time we observed that the deep crater, measuring 3 cm., had filled in and was in the process of epithelization.

#### COMMENT

A brief summary of our data demonstrates that where the jejunum was anastomosed to the pyloric valve and the alkaline contents diverted away from the gastrojejunal anastomosis ulcers formed with regularity in each experiment. When the same procedure was used in ten dogs and three fourths of the circumference of the longitudinal and circular muscles was removed ulcers of the pylorus developed in only three animals. No ulcers were found in the part of the jejunum with the muscle layers denuded. In two dogs, in addition to the ulcer of the pylorus, there were definite ulcers exactly where the muscle began its intact course, or about 10 cm. from the pyloric valve. Again, in two other dogs no ulcers were found except where the normal muscle began its course, or about 10 cm. from the anastomosis of the pyloric valve. If one remembers that most of the experimental ulcers arise at the jejunum, separated from the pyloric valve by only 1 or 2 mm., this observation becomes most interesting (figs. 5 and 7).

In the second series of experiments we anastomosed the ileum to the Pavlov pouch according to the method of Matthews and Dragstedt<sup>3</sup> and stripped the muscle layers of the ileum for a distance of about 10 cm. (fig. 4). Ulcers developed in only one of six animals. This ulcer was found in a part of the ileum with its musculature intact distal to the part of the ileum denuded of its musculature. In view of the findings of Matthews and Dragstedt, the absence of ulcers in our experiments adds support to the observations already recorded.

Of four animals undergoing the Exalto short-circuiting operation, exclusion of a large distal part of the stomach and also an entero-anastomosis opposite the gastro-enterostomy, none had ulcers (fig. 2). Without an entero-anastomosis such a procedure produces ulcers in from 75 to 100 per cent of experiments. The number of animals in the last series is small but nevertheless suggestive, particularly if we consider that in the dog with the huge ulcer there were definite signs of healing following the entero-anastomosis near the ulcer. We have also observed that in most of our animals in which the longitudinal and circular muscles were removed in the jejunum or the ileum and subjected to the action of acid gastric juice the mucosa was pale in the area of the small intestine in which the muscle layers were stripped. Where the muscle layers were not stripped the mucosa was red and injected.

In recent publications Steinberg and Proffitt<sup>6</sup> and Steinberg<sup>8</sup> have reported numerous experiments in which it was demonstrated that the corrosive action of acid pepsin in the presence of certain mechanical factors produces peptic ulcers. It was pointed out that the muscular pyloric part of the stomach propelling the acid contents may be responsible for the actual localized trauma of the jejunum. An impediment in the form of a kink in the distal loop of the jejunum or a narrow gastro-intestinal opening favors the development of a jejunal ulcer. These procedures cause a delay in the emptying time and an increased acidity of the stomach contents. The ulcer found immediately in front of the kink would also demonstrate that there is a direct mechanical trauma determining the location of the ulcer. In the same publication Dr. Steinberg has mentioned the fact that the spastic conditions of the small intestine may be directly related to the etiologic factors in the experimental production of peptic ulcers. The predisposition of the subject, based on the neurogenetic theories which may influence the degree of psychic secretion, and the motility of the gastro-intestinal tract were also mentioned. It was pointed out how difficult it is to estimate the chemical and mechanical factors in some of the experiments.

In view of our findings in the present experimental work, how may we explain the absence of jejunal ulcer where the muscle layers are stripped?

Boldyreff<sup>9</sup> was the first investigator to point out that no matter how high the degree of acidity in the stomach is, the duodenum will not tolerate an acidity higher than 0.15 per cent. Burget and Steinberg,<sup>10</sup> Steinberg, Brougher and Vidgoff,<sup>11</sup> and, lately, Elman<sup>12</sup> have corroborated Boldyreff's work. Cannon<sup>13</sup> has observed that acidity on the duodenal side will close the pylorus. All these observations are important and suggest that when the acid is of a certain concentration the intestinal muscles contract and hold the acid until it is neutralized by some known or unknown factors. This speculation we are now following up by actual experimentation; we hope to report on it at a later date. The intestine with its muscle stripped is not able to contract. When acid of sufficient strength reaches the part of the intestine in which the muscle begins its intact course, a contraction takes place, and in a manner as yet not altogether explained a localized trauma takes place, producing an inflammation of the mucosa or an ulcer.

In our present experiments it would be impossible to imagine a propelling force producing ulcers where the muscle began its intact course, since this part of the intestine was separated from the pylorus by 10 cm. of jejunum with its muscle stripped and therefore lacking peristaltic activity. In one of our experiments two small chronic "kissing ulcers" occurred exactly as we see them in the duodenal cap. Perhaps the lumen contracted in such a manner that it exposed two small areas of the mucosa to the acid pepsin.

As already mentioned, when the muscle of the jejunum is intact most of the experimental ulcers are found immediately distal to the pylorus and separated from it only by a narrow strip of jejunal mucosa. This may be due to the fact that the part of the intestine which first receives the acid holds it in check until it is partially neutralized and therefore becomes harmless to the jejunal mucosa distal to the pylorus. This may also explain why we found ulcers only where the muscle began its normal course and not distal to this area. It must nevertheless

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9. Boldyreff, W.: The Self-Regulation of the Acidity of the Gastric Juice, *Quart. J. Exper. Physiol.* 8:1, 1915.

10. Burget, G. E., and Steinberg, M. E.: The Regurgitation of Intestinal Contents in Normal Dogs and Dogs with Posterior Gastro-Enterostomy, *Am. J. Physiol.* 60:308 (April) 1922.

11. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations, *Arch. Surg.* 15:749 (Nov.) 1927.

12. Elman, Robert: Acidity in Duodenal Ulcer and Pyloric Obstruction, *Surg., Gynec. & Obst.* 49:34, 1929.

13. Cannon, W. B.: The Mechanical Factors of Digestion, London, Edward Arnold & Co., 1911.

be mentioned that occasionally a few ulcers may be found a few centimeters away from the pylorus in the control experiments in which the muscle walls are left intact. It is possible that our findings may partially explain the fact that Dragstedt and Vaughn<sup>14</sup> were not able to produce ulcers in most of their experiments with parts of the intestine implanted in the stomach wall. Such a procedure would eliminate the ability of the implanted loops of the small intestine to contract and would produce a narrow lumen. Our observation does not exclude the possibility of the mechanical factors brought forward in a previous publication (Steinberg and Proffitt;<sup>6</sup> fig. 6).

In view of the theories of von Bergmann, Cushing and others concerning the neurogenic factors related to the gastroduodenal ulcers, our findings become most interesting and significant. At this time we are not ready to enlarge on all of the factors which may determine the formation of an ulcer. The sequence of hypermotility, spasm and degree of acidity are interrelated, and it is difficult to evaluate each factor separately. Matthews and Dragstedt<sup>2</sup> introduced a valve into the pylorus and were able to produce ulcers in four of eight transplants of intestine into the stomach. These investigators believed that it was the lack of regurgitation of the alkaline contents and therefore the heightened degree of acidity which were responsible for the formation of ulcers. On the other hand, it is our opinion that a valve fixed at a pyloric opening will also act as a foreign body, causing irritation and hypermotility. A valve 20 cc. below the gastrojejunal anastomosis would also be responsible for the irritability of the gastro-intestinal tract above this artificial impediment. We believe that the factor of the degree of acidity is of great importance, but we also believe that spasm and hypermotility are equally important.

#### SUMMARY AND CONCLUSIONS

Sixteen dogs operated on according to several technics which regularly produced ulcers failed to show evidence of ulcerations in the area of the jejunum, which was stripped of about three fourths of its longitudinal and circular muscle layers. In three dogs ulcers developed in the jejunum separated from the pylorus by about 1 or 2 mm. of normal jejunal mucosa. In five dogs ulcers were found in the jejunal mucosa distal to the area stripped of its muscle, exactly where the intact layers of muscle began their normal course, or about 10 cm. from the gastrojejunal anastomosis. The last observation according to our knowledge has never been made before.

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14. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies; the Resistance of Various Tissues to Gastric Digestion, *Arch. Surg.* 8:791 (May) 1924.

In four dogs with a large exclusion operation according to Devine and an Exalto short-circuiting operation, which regularly produce ulcers, ulcers did not develop when an entero-anastomosis was made opposite the gastro-enterostomy.

The *modus operandi* in our experiments which prevented ulcerations appears to be the release of spasm through the stripping of the jejunal muscle wall or through an additional entero-anastomosis opposite the gastro-anastomosis. Since in most of the experiments of the present series with the muscle layers stripped there was no *vis à tergo*, we believe that a certain degree of acidity depending on the particular area of the intestine causes it to contract until the degree of acidity is reduced to a certain strength. A prolonged contact of unneutralized pepsin with intestinal mucosa causes an ulcer, provided there is also present the possibility of the narrowing of the lumen through spasm. This, however, does not exclude some of the other mechanical factors elaborated by one of us (M. E. S.).

Our observations support the neurogenic theory as an important factor in the etiology of ulcerations of the upper gastro-intestinal tract.

# MALIGNANT LYMPHOMA OF THE GASTRO- INTESTINAL TRACT

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Malignant lymphoma is a neoplasm that arises from the lymphatic tissues and is due to a proliferation of atypical cells of the lymphatic series. They extend not only locally and regionally, but often eventually to distant organs. Frequently they assume the forms of diffuse infiltrations, and some authors believe that in such cases a continuous lymphatic connection, including a retrograde process, can be demonstrated between the primary and secondary growths. Other forms are diffuse at the onset, and a definitely localized primary focus cannot be ascertained. Changes in the circulating blood stream are either absent or of no differentiating value, with the exception of a terminal leukemia seen in some cases.

The lesions have been extensively classified, but recently there has been a tendency among pathologists to consider these various conditions as different manifestations of the same pathologic process. Thus, the term malignant lymphoma has come into use.

There is one manifestation of the disease which is of special interest to the surgeon, and that is the group in which the primary nidus is well localized and metastases are only local or regional, though terminally more distant extensions are occasionally seen. This type of malignant lymphoma is usually placed in the lymphosarcoma group. Since 1930, six such cases, all with localization in the gastro-intestinal tract, have come to operation in the surgical service at the University Hospital. A report of the six cases is the object of this paper.

As will be noted in the reports, symptomatically the lesions are not characteristic, and a correct preoperative diagnosis was not made in any case. In cases previously reported in the literature, the age of the patients varied from  $3\frac{1}{2}$  to 85 years. As a rule the average age incidence is from fifteen to twenty years below that of carcinoma of the gastro-intestinal tract. However, because of the wide variance of age in both types of lesions, this point is of little value in arriving at a differential diagnosis.

Pathologically, lymphomas differ from carcinoma in that they arise in the submucosa and infiltrate the submucosa and muscularis. Ulceration, though not infrequent, is often absent, and when it occurs, is due to necrosis from pressure and loss of blood supply rather than to neoplastic invasion.

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In the stomach, the lesions when first seen vary from a small, well localized nodule to a diffuse infiltration of practically the entire wall of the stomach. The wall may simply be thickened, which is the usual condition, or sessile and polypoid masses may obtain. Frequently, the tumors are situated in the antrum, but usually far enough from the pylorus that obstruction by tumor is uncommon. The cardia is rarely involved except in the diffuse lesions. The lesion most commonly occurs on the lesser curvature. Secondary lesions are common, and usually occur in the form of local involvement of the regional lymph nodes. Extension to the liver is unusual.

In the small intestine, the lower part of the ileum is most commonly involved, though lesions have been reported to occur in any part of the small intestine from the duodenum to the terminal portion of the ileum. The lesion may be diffuse, nodular, sessile or polypoid. The tumor, arising in the submucosa, early extends through and destroys the muscularis. Metastasis to the regional lymph nodes occurs early. Aneurysmal dilatation of the intestine at the site of the neoplastic invasion is frequent. This is due to destruction of the muscle fibers with resulting separation or to involvement of the submucosa, with subsequent effect on its plexus of nerves. Obstruction is not frequent. When it occurs, it is usually late in the disease and is due to pressure from the enlarged mesenteric glands or as a result of fibrosis, which may occur late in the disease. DeNoyelles<sup>1</sup> reported a case of a polypoid malignant lymphoma protruding into the lumen and resulting in obstruction. Partial obstruction occasionally occurs when a large segment is involved as a result of loss of peristalsis. Intussusception is fairly frequent, the tumor occupying the apex of the invaginated loop.

In the large intestine, the lesions are similar to those in the small intestine, though the lumen is not often encroached on. The most common site of occurrence in this section is at the cecum, though lesions may also occur in any portion of the large intestine. One in this series was mistaken for carcinoma of the rectum.

Results of the laboratory examinations are in no way distinctive. The roentgen-ray diagnosis following ingestion of a barium sulphate mixture is usually carcinoma, though a diagnosis of gastric ulcer is sometimes made. In a fair number of cases the examination reveals no abnormality. In the earliest stage, that is, when the submucosa alone is involved, the lesion does not interfere with the muscular function of the stomach. Ulceration of the mucosa is not an early pathologic change. Holmes, Dresser and Camp,<sup>2</sup> reporting eight cases studied roentgenologically, stated that they diagnosed only one case preoperatively, and in that there was peripheral involvement of lymph nodes, and one

1. DeNoyelles, P. L.: Lymphosarcoma of the Intestine, *Ann. Surg.* **76**:229, 1922.

2. Holmes, G. W.; Dresser, Richard, and Camp, J. D.: *Lymphoblastoma*, *Radiology* **7**:44, 1926.

of the nodes was taken for biopsy. Two of their cases showed a normal roentgenologic appearance. Observations on the remaining six were: sluggish, irregular peristalsis which did not pass over the site of the lesion; a filling defect, usually annular, and gastric stasis. In brief, the roentgenologic appearance does not differ from carcinoma, except in some cases in which peristalsis is not interfered with to the extent usually seen in carcinoma of the stomach. Roentgen examination is of little value in the diagnosis of most lesions involving the small intestine, the patency of the intestine and the lack of early ulceration militating against a diagnosis. It has been suggested that an examination every one or two hours after the ingestion of a barium sulphate meal may aid by determining a temporary retardation of the flow of barium.

#### REPORT OF CASES

The patients in the following six cases were operated on in University Hospital.

CASE 1.—*History*.—R. I., a woman, aged 58, was first seen in the medical service of the University Hospital complaining of gas and heaviness in the stomach. Nine months before admission she noticed that she was becoming pale. There had been a gradual loss of weight in the preceding two months, from 98 to 90 pounds (44 to 40 Kg.), with considerable loss of strength. There was no history of hematemesis or melena.

Physical examination revealed a thin, undernourished, asthenic woman. The heart and lungs were not remarkable. The blood pressure in millimeters of mercury was 130 systolic and 75 diastolic. The spleen was palpable. There was a rather indefinite abdominal mass, not tender, just above and to the left of the umbilicus.

On laboratory examination the urine showed a trace of albumin. The blood count showed: red cells, 4,000,000 per cubic millimeter; white cells, 7,100, and hemoglobin, 65 per cent. The differential count was essentially normal. A fractional gastric analysis revealed no free acid until histamine was given, when it reached 10. The Wassermann reaction was negative. Visualization of the stomach by means of a barium meal revealed evidence of a filling defect within the lumen of the stomach in the region of the pars pylorus which had a more or less loculated appearance, and suggested the presence of multiple polypi.

A tentative diagnosis of gastric polyposis was made, and after suitable pre-operative preparation an exploratory operation was performed on March 30. In the prepyloric end of the stomach was a mass about the size of a lemon. It was elastic and spongy, and could be moved through a fairly wide excursion, though it did not extend down to the pyloric ring. There was no evident pathologic change in the wall of the stomach. There were many lymph nodes in the greater and lesser omenta, the largest being the size of a hickory nut. Two were removed for microscopic study. The lower end of the stomach was then resected, a Billroth I technic being used. The patient left the operating table in good condition. Soon, however, she began to raise small amounts of blood. This was not controlled by giving blood in the buttock. A transfusion was given, but she did not rally, and died on April 1. Permission for a postmortem examination was not obtained.





Fig. 1 (case 1).—The loculated filling defect in the pars pylorus after the ingestion of barium. The stomach was entirely empty in six hours.



Fig. 2 (case 1).—The resected portion of stomach. The arrows point to two sectioned lymph nodes.

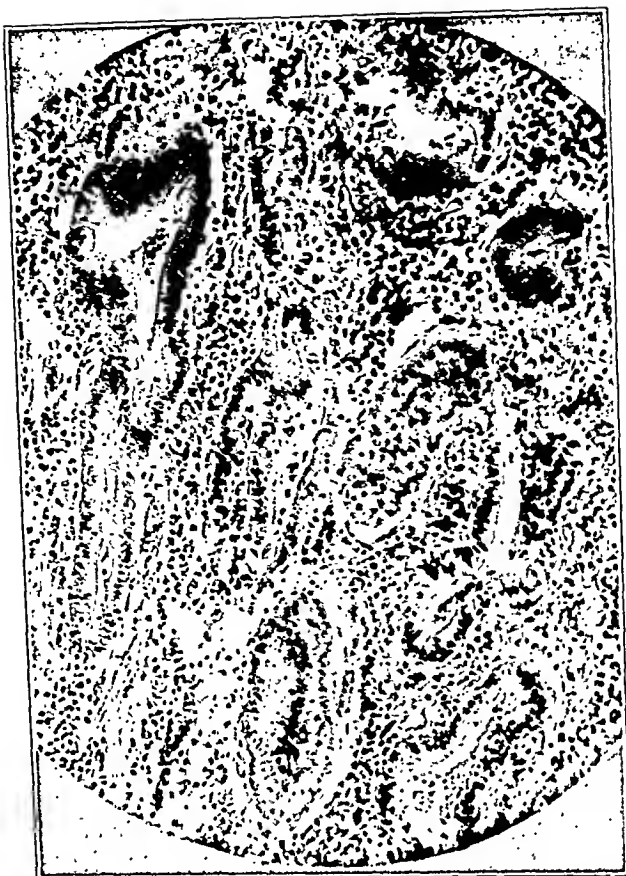


Fig. 3 (case 1).—A section from the polypoid mass showing the numerous alveoli and tubules in the adenoma. Many inflammatory cells are present in the supporting connective tissue.

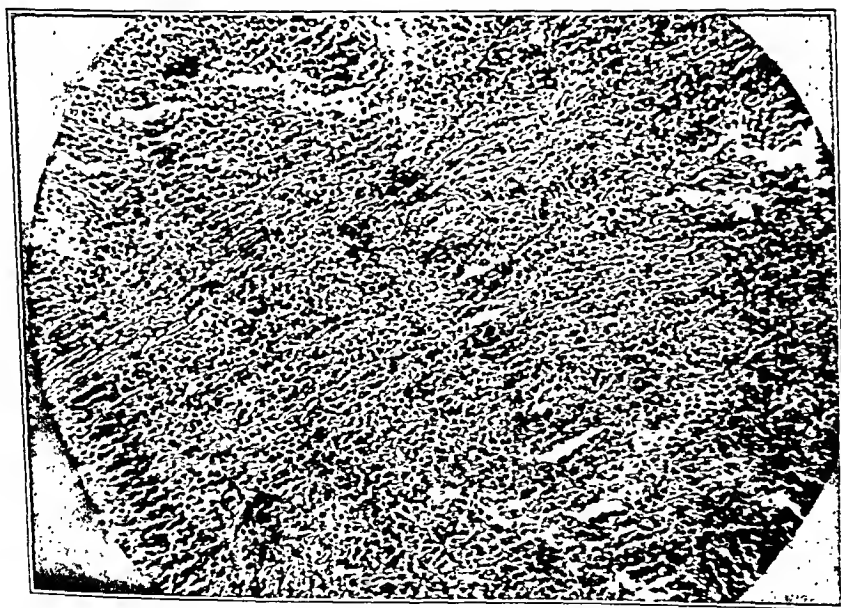


Fig. 4 (case 1).—In the wall beneath the adenoma are the invading neoplastic cells which are uniform and of the plasma cell type. Invasion into the muscular layer, with separation of the fibers, is a prominent feature.

Microscopically the polypoid mass revealed numerous alveoli and tubules embedded in a loose, vascular fibrous connective tissue. In the surrounding connective tissue were many plasma cells and some lymphocytes and eosinophils. A section through the wall of the stomach at the base of the mass showed marked infiltration of plasma cells, so great that in some places the structure of the wall was obliterated. Sections of the lymph nodes showed replacement of the normal architecture by plasma cells and a few small lymphocytes and endothelial cells. The diagnosis was adenoma of the stomach and malignant lymphoma of the stomach, with metastases to the regional lymph nodes.

CASE 2.—G. M., a man, aged 20, was first admitted to the medical service of the University Hospital complaining of pain in the upper part of the abdomen,

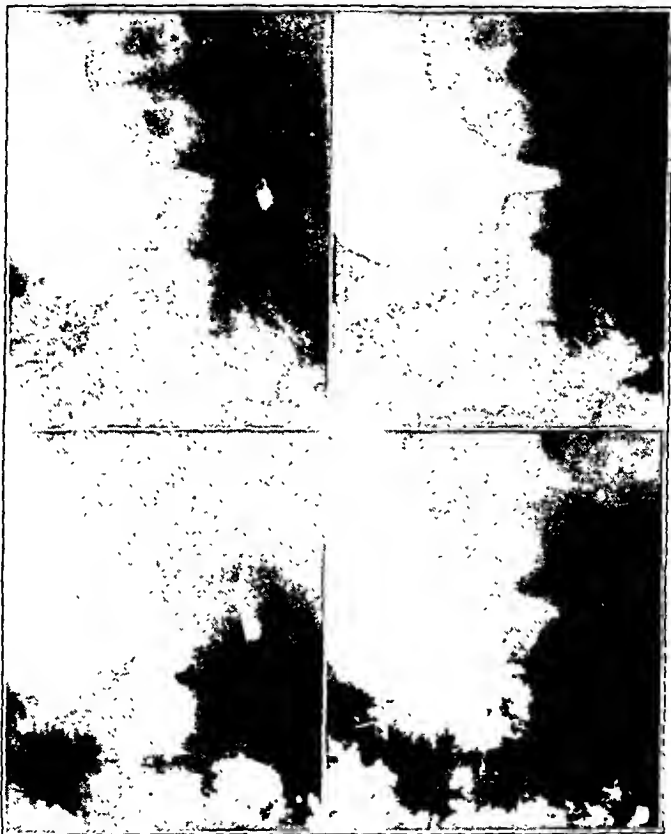


Fig. 5 (case 2).—Following ingestion of a barium mixture this film, taken postoperatively, shows the functioning gastrojejunostomy stoma and a persistent defect in the region of the pylorus.

vomiting and loss of weight. The abdominal pain began about one year before admission as a dull discomfort, present most of the time, but increased by eating. There had also been frequent vomiting after eating and a loss of 20 pounds (9 Kg.). One year before admission, there was an injury with possible fracture of a vertebra and loss of sensation in the legs for forty-eight hours.

Physical examination in the medical service and later in the surgical service revealed nothing relevant except tenderness over the first lumbar vertebra and slight rigidity and tenderness in the epigastrium.

Laboratory examination revealed: red blood cell count, 4,900,000 per cubic millimeter; white blood cell count, 7,600, and hemoglobin, 85 per cent. The

differential blood count was normal. Urinalysis gave negative results. A fractional gastric analysis revealed a slight hypo-acidity, the high level of free acid being 15 and the high level of total acid being 30. Examinations of stools revealed a positive Meyer reaction on two occasions. Visualization of the stomach by means of a barium meal revealed a persistent niche on the greater curvature in the pyloric region, suggesting a penetrating type of ulcer. Films of the chest, spine and colon were essentially normal.

A positive diagnosis could not be made, the two major probabilities being carcinoma of the stomach and gastric ulcer. It was decided to place the patient on an ulcer regimen for one month, and if no improvement occurred to perform an exploratory operation. This was done, the patient receiving no relief from his symptoms.



Fig. 6 (case 2).—Infiltration of the submucosa with neoplastic cells and the displacement of the gastric glands were prominent features. Note that the gastric mucosa in this section is intact. The type cell of the neoplasm is the lymphocyte.

At operation, on November 30, no lesion was found at first in the pyloric region to account for the roentgen-ray findings. However, the entire wall of the stomach was thickened and less elastic than normal. Along the greater curvature of the stomach several enlarged lymph nodes, one the size of a hazelnut, were found in the mesentery. It was felt that visualization of the inside of the stomach was necessary to arrive at a conclusion, so a 2 inch (5 cm.) incision was made longitudinally near the pylorus on the anterior wall. Both muscular and submucosal layers were definitely thickened and inelastic, and a sensation of friability was obtained. There were several large, irregular areas where the mucosa seemed to be lost or superficially ulcerated. In one or two areas there was heaping up of mucosa. The roentgen-ray findings were explained on viewing the interior of the stomach. A small pouching had taken place at the site of the niche. This was due to the fact that a small area of the wall of the stomach was less involved than

the area surrounding it. A portion of the wall of the stomach was removed for biopsy, the incision closed and a posterior gastro-enterostomy done.

Microscopic examination of the biopsy specimen revealed areas of ulceration of the mucosa. The submucosa was packed with cells of the lymphatic series, both adult and blast cells being noted. Mitotic figures were numerous. There was little stroma present. The gastric glands were practically completely replaced by the lymphatic cells, but the tissue seemed fairly well limited to the submucosa, the muscle layer showing only a slight lymphocytic infiltration. Sections of the lymph nodes showed chronic lymphadenitis. The pathologic diagnosis was malignant lymphoma of the stomach.

The postoperative course was essentially uneventful. After receiving the pathologic report, a course of irradiation therapy was given, and the patient was discharged. He was seen again, three months after operation, at which time he felt much better, though he had vomited on several occasions. He had gained 20 pounds. Visualization of the stomach by means of a barium meal showed an increase in the size of the filling defect. The gastro-enterostomy stoma was functioning well. He was given a course of irradiation therapy. He next returned eight months after the operation. At that time there were no gastro-intestinal symptoms, and the patient was doing manual labor. Visualization of the stomach by means of a barium meal showed some regression in the size of the filling defect and a functioning gastro-enterostomy stoma. He was again given a course of irradiation therapy. He was last seen fifteen months after the operation, at which time he was in the best of health and had no complaints. The condition of the stomach, however, remained unchanged. He was given another course of irradiation therapy at that time.

CASE 3.—L. S., aged 4, was admitted to the surgical service of the University Hospital on March 10, 1932, with a history of severe pain in the midepigastrium beginning on Oct. 13, 1931, which was accompanied by nausea and vomiting. On October 15 he vomited continuously for two hours. He was given tincture of belladonna, with relief. Since then he had had frequent attacks of vomiting and cramplike pain in the upper portion of the abdomen, and at the time of admission the pain was nearly continuous.

Physical examination revealed a fairly well developed and well nourished Mexican boy. The tonsils were moderately enlarged. There was a rachitic rosary. The abdomen was slightly distended. A mass about 10 cm. in length could be palpated, lying transversely in the abdomen at the level of the umbilicus. There was slightly diffuse abdominal tenderness.

Laboratory examination revealed: red blood cell count, 4,600,000 per cubic millimeter; white blood cell count, 10,000; hemoglobin, 80 per cent and differential count, normal. Urinalysis gave negative results. Visualization of the large intestine by means of a barium enema and a six hour examination after the ingestion of a barium meal revealed evidence of an intussusception extending nearly to the splenic flexure of the large intestine.

He was operated on on March 11. An intussusception involving the large intestine and terminal portion of the ileum and extending as far as the splenic flexure was found. The intussusception was reduced with ease. After reduction, a striking change remained at the ileocecal junction. Involving the wall of the terminal portion of the ileum was a band of firm, inelastic grayish-white tissue, about 1 inch (2.5 cm.) wide. This segment of the intestine was several times thicker than the wall proximal to it. The thickening extended onto the wall of the cecum toward the base of the appendix. In the terminal 3 inches (7.6 cm.)

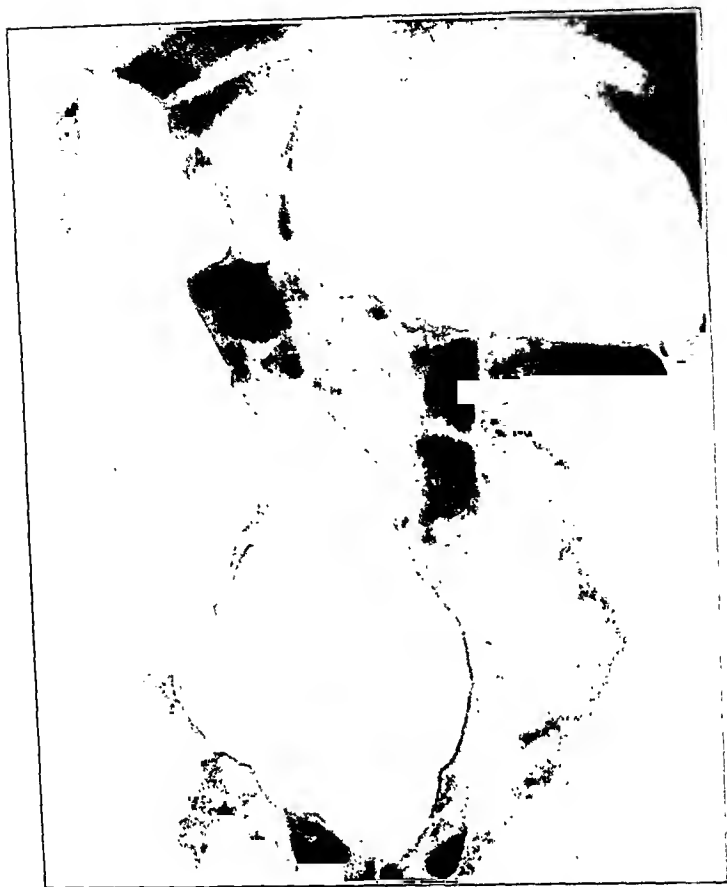


Fig. 7 (case 3).—A barium mixture was injected into the large intestine. This film reveals what was thought to be localized areas of spasm, but it was an intussusception.

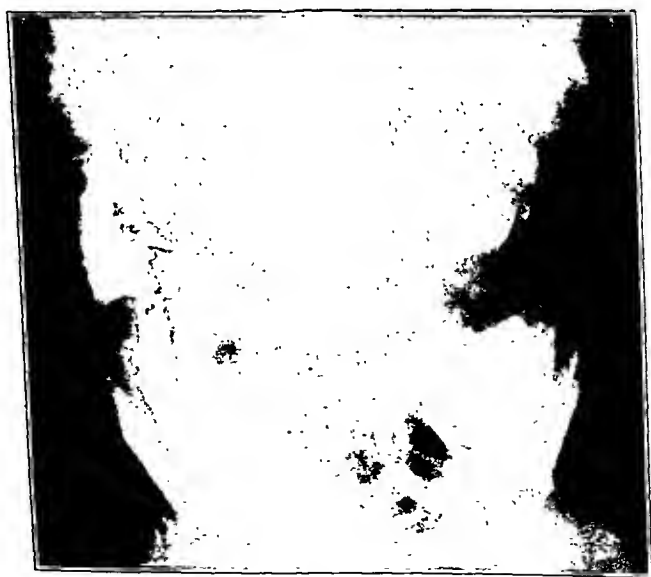


Fig. 8 (case 3).—This film, taken twenty-four hours following the ingestion of a barium mixture, is typical of intussusception into the large intestine.

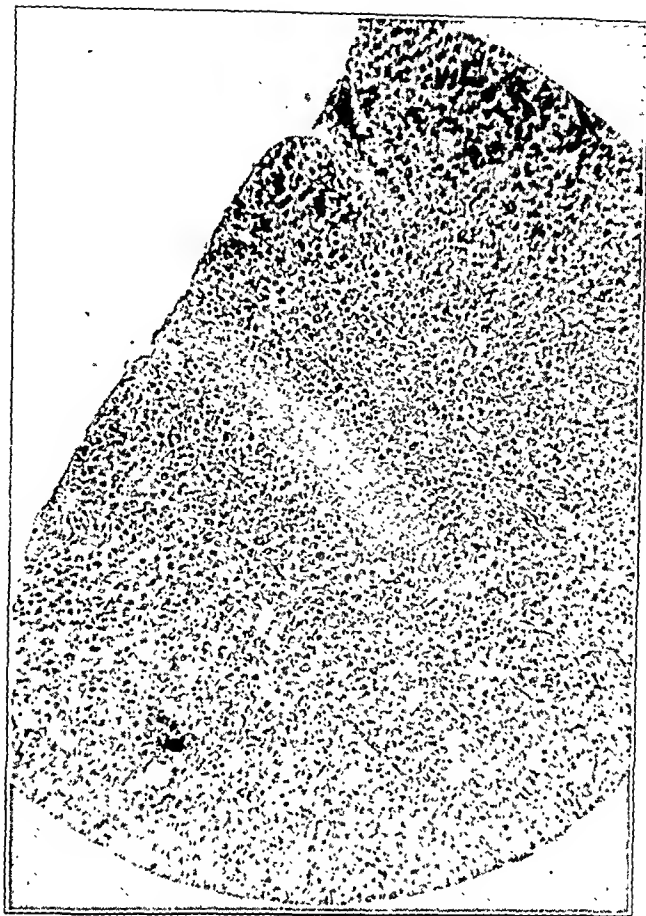


Fig. 9 (case 3).—The cellularity is well illustrated. Little stroma can be seen. The mucosa is ulcerated, but is intact in other areas.



Fig. 10 (case 3).—The muscularis of the ileum is being invaded by the neoplasm, with a separation of the fibers. The resulting loss of tone is a factor in the local dilatation of the intestine.

of ileum, what was thought to be a mass was felt in the lumen. A resection of 5 inches (12.7 cm.) of cecum and 4 inches (10.1 cm.) of the terminal portion of the ileum was done, and a lateral anastomosis made.

On opening the ileum the portion thought to have been a mass was found to be made up of nodular areas of thickening of the submucosa. Areas of ulceration were present. In the region of the band, the whole wall was firm, inelastic, grayish white and very cellular. Microscopically, the mucosa was ulcerated for the most part. Cells of the lymphocytic series formed the base of the ulcer and extended down into and through the muscular layer to the serosa. Mitotic figures were numerous. The cells were packed close together, and laid in a thin connective tissue stroma. The pathologic diagnosis was malignant lymphoma of the ileum and ileocecal junction.

The boy had a fairly uneventful postoperative course, and was discharged on April 1. Although we requested his return he did not come back to the hospital. A letter from his father on July 10, 1933, informed us that the boy was in excellent health and in no way appeared to be ill.

CASE 4.—J. C., a man, aged 23, had been admitted to the University Hospital four times previously to his admission on June 26, 1931, for control of diabetes mellitus and removal of bilateral cataracts. He was admitted to the genito-urinary service complaining of a mass in the right side of the abdomen, first noticed in February 1931. At the time the mass was first noticed he was constipated. There was no pain, but the tumor was somewhat tender. In March 1931, following his evening meal, he became nauseated, and diarrhea developed which lasted for twenty-four hours. He had twelve watery stools. He had no further discomfort following this episode, but he noticed that the mass became tender when he was constipated. A cystoscopic examination revealed the mass to be intraperitoneal, and it was thought to be in the hepatic flexure of the colon. He was then transferred to the surgical service.

Physical examination revealed a well developed and well nourished white man. There was mild pyorrhea alveolaris. Both pupils were irregular and fixed in places, and both corneas were scarred. A mass, firm and freely movable, was found in the right side of the abdomen. The lower margin was about two fingerbreaths above the crest of the ilium. It was somewhat egg-shaped, and could barely be felt posteriorly. On deep inspiration it moved 4 cm. downward. It was slightly movable in lateral and mesial directions. Fluid was demonstrable in the peritoneal cavity.

Laboratory examination revealed: red blood cell count, 5,200,000 per cubic millimeter; white blood cell count, 6,800, and hemoglobin, 80 per cent. Urinalysis and the Wassermann test gave negative results. Visualization of the large intestine by means of a barium enema revealed a marked irregularity and spasticity involving the ascending colon.

He was placed on diabetic management, and an exploratory laparotomy was performed on July 3. A moderate amount of clear straw-colored fluid was found in the peritoneal cavity. In the region of the cecum a mass the size of a large orange was encountered. This involved the terminal portion of the ileum for 3 inches, as well as the cecum. The wall was thickened and somewhat reddish. The mass involved the serosa of the cecum over one area the size of a silver quarter. Here the wall was firm and inelastic. There was some infiltration into the mesentery, but no involved lymph nodes were encountered. The lesion resembled chronic hyperplastic tuberculosis. A resection of the terminal ileum and



large intestine, up to the proximal 4 inches of the transverse colon, was performed and a lateral anastomosis made.

On making an opening into the cecum, the mass was found to arise from the submucosa. The mucosa was ulcerated in certain areas. The muscularis was infiltrated, and the cut section of the tumor was grayish white and cellular. Some enlarged glands were found in the mesentery. Microscopically, the tumor consisted of lymphoblasts packed closely together. Many mitotic figures were present. The stroma was scant. In one area, the neoplasm extended through the muscularis to the serosa. The mesenteric lymph nodes showed a similar replacement. The pathologic diagnosis was malignant lymphoma of the cecum, with metastases to the mesenteric lymph nodes.

The postoperative course was complicated by cellulitis of the scrotum which extended up over the abdomen onto the chest wall. On July 23 the cellulitis was

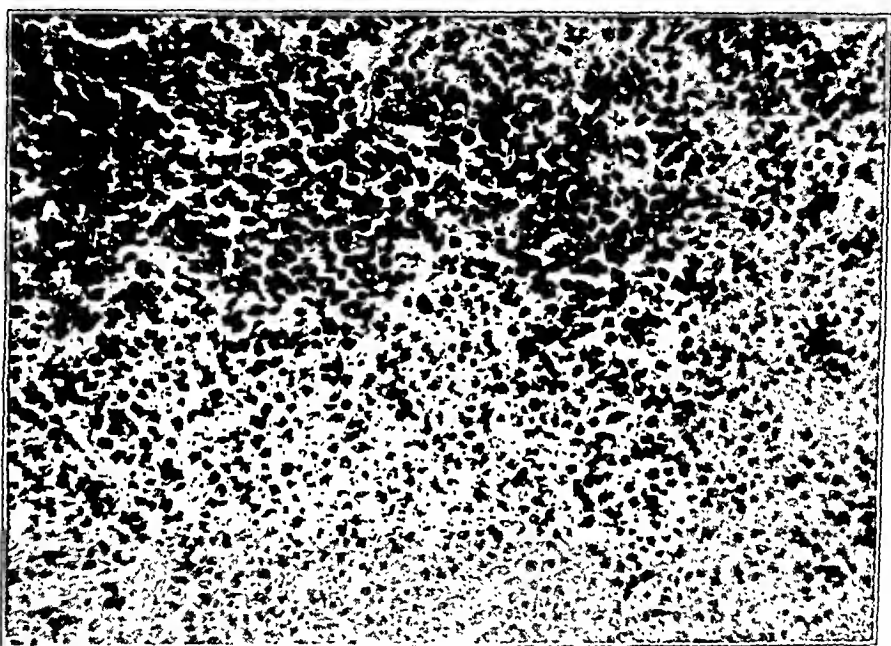


Fig. 11 (case 4).—High power photomicrograph showing the cellularity of the neoplasm. Only a small amount of reticulum is present. Numerous mitotic figures are present.

apparently controlled. However, on July 27, spontaneous hypoglycemia developed which did not respond to therapy, and the patient died. Permission for a post-mortem examination was not obtained.

CASE 5.—B. R., a woman, aged 42, was admitted to the surgical service of the University Hospital on June 19, 1932. For six months she had noticed an increasing weakness, and had lost 20 pounds. Two months before admission she was seized by a severe cramping pain, beginning just to the right of the umbilicus and radiating down to the symphysis and up beneath the right costal margin. Since then, she had similar attacks every three or four days. Residual tenderness was always noticed in the right upper quadrant of the abdomen. For six weeks before admission she had also had several attacks of dull pain in the right upper quadrant which would radiate around to the back. She was occasionally nauseated, but never vomited. There was no jaundice or bloody stools.

Physical examination revealed a well developed but emaciated white woman. There was slight enlargement of the right lobe of the thyroid gland. There was moderate spasticity of the entire right side of the abdomen. A palpable and freely

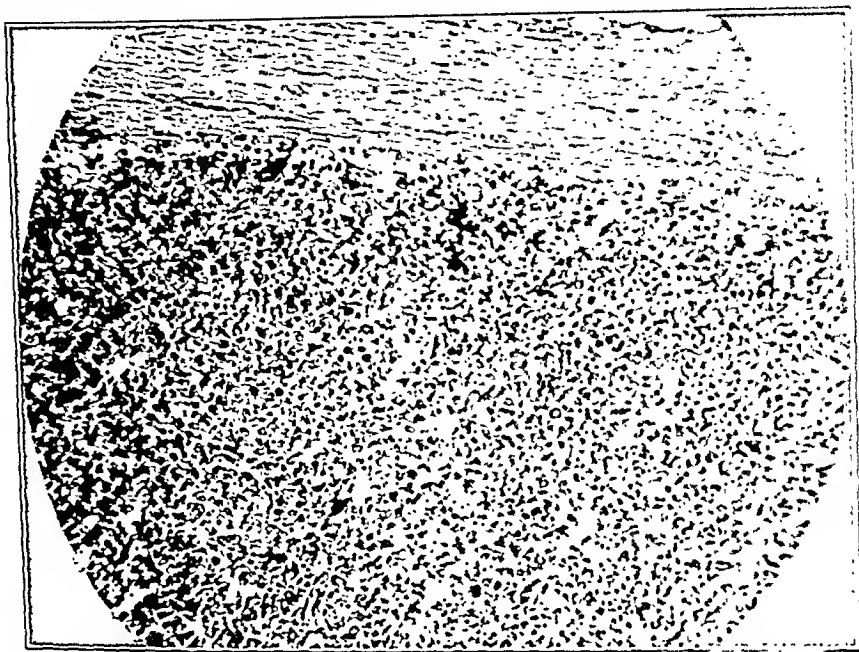


Fig. 12 (case 5).—The structure of the lymph node has been replaced by neoplastic tissue.

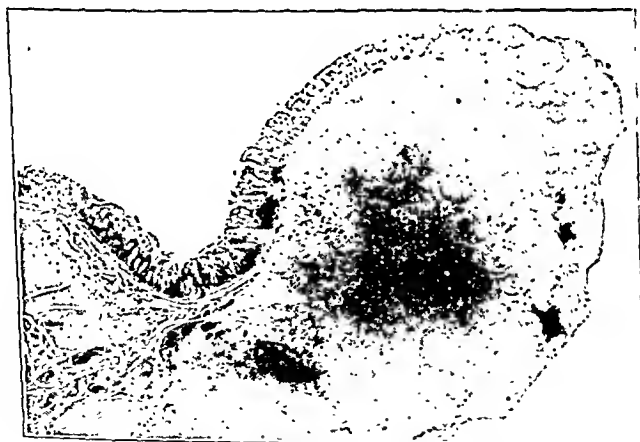


Fig. 13 (case 5).—Photomicrograph showing extension in the submucosa. The mucosa is intact for a considerable distance over the tumor.

movable mass was present in the right lower quadrant, which was slightly tender. There was slight tenderness in the region of the gallbladder.

Laboratory examination revealed: red blood cell count, 3,100,000 per cubic millimeter; white blood cell count, 6,700, and hemoglobin, 60 per cent. The

Wassermann reaction was negative. Visualization of the large intestine by means of a barium enema revealed a redundant ptotic colon. A cholecystogram revealed a nonvisualizing gallbladder.

An exploratory laparotomy was performed on June 27. All the abdominal organs lay unusually low. The cecum was delivered through the incision. In its mesentery was a mass about the size of a tennis ball, which was made up of enlarged lymph nodes. An intussusception of the distal ileum into the cecum was noted, and in the lumen of the cecum could be felt a mass, roughly globular, but irregular in contour and about 2 inches in diameter. A resection of the terminal portion of the ileum, cecum and ascending colon was done, and a lateral anastomosis made. All lymph nodes were thought to have been removed. There were some adhesions around the gallbladder, but when these were separated the gallbladder appeared to be normal.

When the cecum was opened, the mucosa over the palpable mass was not ulcerated. On cut section it was grayish white and homogeneous. The mass seemed to arise from the submucosa, and did not appear to invade the muscularis. Microscopically, the neoplasm consisted of a compact, structureless, cellular neoplasm which involved the submucosa and invaded the muscularis. The cells were lymphocytes, and many mitoses were present. The lymph nodes showed a similar histologic picture. The pathologic diagnosis was malignant lymphoma of the cecum, with metastases to the mesenteric glands.

The postoperative course of the patient was uneventful. She was not seen again until fifteen months after operation. At that time she presented no complaints and no evidence of a recurrence. Visualization of the stomach by means of a barium meal and visualization of the large intestine by means of a barium enema revealed essentially normal organs. The anastomosis was functioning well.

The patient recently returned to the hospital (Sept. 15, 1934) in a much debilitated condition and with palpable intra-abdominal masses.

CASE 6.—E. E., a woman, aged 70, was admitted to the surgical service of the University Hospital on Dec. 29, 1932, complaining of pain in the rectum and bloody stools. She had always been well until April 1932, when she passed some bright red blood by the anus. This happened again the following July. Three months previous to admission she began to have pain with the passing of stools. There had been no change in the character of the stools. She had had hemorrhoids for a number of years. For the past year she had had a dull aching pain in the lower part of the back. She had lost 20 pounds in the previous year. There was a history of carcinoma of the stomach in the patient's mother and carcinoma of a breast in one of the patient's sisters.

Physical examination revealed a fairly well developed and well nourished white woman, who was not acutely ill. There was bilateral middle ear deafness. There was a cauliflower-like mass about the size of a small fist in the rectum on the right. This was freely movable.

Laboratory examination revealed: red blood cell count, 3,950,000 per cubic millimeter; white blood cell count, 9,500 and hemoglobin, 60 per cent. Urinalysis and the Wassermann test gave negative results.

A diagnosis of carcinoma of the rectum was made. On December 31, an exploratory operation was performed through a left lower transrectus incision. The lesion did not extend above the pelvic floor, and no evidence of metastases was found, so a loop of the sigmoid flexure was brought out through the incision, the loop subsequently being opened on Jan. 9, 1933. On January 24, she was again operated on, a perineal resection of the distal sigmoid flexure and rectum being done. No evidence of invasion into the surrounding tissues was noted. Following

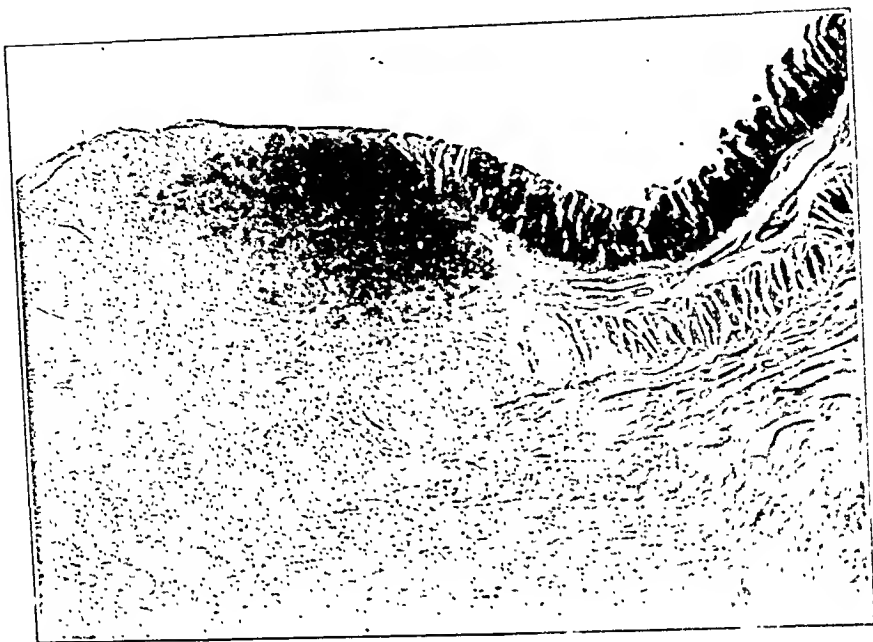


Fig. 14 (case 6).—The edge of the tumor of the rectum. The cells have invaded through the muscularis.



Fig. 15 (case 6).—The edge of the ulcerated mucosa shown in figure 14. Many mitotic figures are present in the bulk of the tumor.

this procedure, the patient progressed satisfactorily, except that there was a profuse and foul discharge for a number of days. She was discharged from the hospital on February 15, with only a small amount of purulent discharge coming from the wound. She did not receive roentgen-ray therapy.

On pathologic examination the mass did not present the cauliflower-like appearance noted on physical examination. This may have resulted from a regression of the tumor following colostomy. The mucosa was ulcerated over the central portion of the mass. On cut section the tumor was grayish white and granular, and apparently invaded through the muscularis. There were numerous lymph nodes in the surrounding fat which appeared to be normal. Microscopically, the mucosa extended up part way along the neoplasm, and gradually faded out into the tumor tissue. The majority of the cells were round cells of moderate size, with an oval, violet-staining nucleus and a pale pink cytoplasm. The cells showed many mitoses. Scattered among them were lymphocytes and many plasma cells. A few eosinophils were present. The tumor had invaded the outer muscular coat. The lymph nodes showed no evidence of neoplasm. The pathologic diagnosis was malignant lymphoma of the rectum.

The patient has not returned to the hospital since the operation. However, a recent letter from her nurse stated that the perineal wound is still draining, the patient is rapidly losing weight and strength and is bedfast.

# SPASM OF THE ORBICULARIS OCULI IN LOCAL TETANUS

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The ordinary development of tetanus in man comprises tonic spasm of the masseter muscles (trismus) with spreading to other groups of muscles (descending tetanus). Occasionally the spasm is initiated in the wounded limb and extends to the whole body (ascending tetanus) or remains localized in the affected member (local tetanus). Spasm or paralysis limited to one or more muscles of the head may be considered a variety of local tetanus.<sup>1</sup>

In reviewing reported cases of local tetanus placed on record prior to the World War and occurring in civil practice, I<sup>2</sup> encountered only four cases, of which I was doubtful;<sup>3</sup> to this number I added a civil case of the monoplegic type developing in a patient who had not received prophylactic antitoxin. During the war the number of cases of local tetanus occurring in inoculated patients rapidly increased, causing an interest among French investigators reflected in the monograph by Courtois and Suffit-Giroux on abnormal forms of the disease. The comparative frequency of local tetanus in military practice was ascribed by Etienne<sup>4</sup> to the neutralization of toxin circulating in the blood stream by the prophylactic injection, with prevention of general manifestations. Francaise<sup>5</sup> believed that the prophylactic injection was not always effective in forestalling the development of local tetanus, since it could not affect the toxin already combined with tissues of the nervous system. Chauvin<sup>6</sup> also subscribed to these views. In the succeeding years of

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1. Rabinovich, G. B.: Experimental Study of Local Tetanus and Its Special Form of Paralytic Head Tetanus, *Klin. med.* **10**:213, 1932.

2. Müller, G. P., and Taylor, K. P. A.: Local Tetanus, *Ann. Surg.* **74**:110 (July) 1921.

3. Axhausen, L.: Ueber lokalen Tetanus beim Menschen, *Deutsche Ztschr. f. Chir.* **78**:265, 1905. Demontmerot, M.: De la forme paraplégique dans le tetanos chronique, Thèse de Paris, 1904. Von Esau, F.: Ein Fall von lokalem Tetanus der Hand, *Deutsche med. Wchnschr.* **36**:706, 1910. Jacobsen, N., and Pease, H. D.: The Serum Therapy of Tetanus, *Ann. Surg.* **44**:321 (Sept.) 1926.

4. Etienne, G.: Tetanos partiels essentiels, *Paris méd.* **29**:91, 1918.

5. Francaise, H.: Tetanos localisé, *Paris méd.* **29**:255, 1918.

6. Chauvin, E.: Les tétanos localisés des membres, *Presse méd.* **26**:295 (June 10) 1918.

the war, the ratio of cases of local tetanus to those of general tetanus became progressively higher. Bruce<sup>7</sup> attributed this increase to the more widespread use of the prophylactic injection and to more frequent recognition of mild and obscure cases.

Ashurst<sup>8</sup> pointed out the similarity between local tetanus and the "experimental" tetanus which had long been observed to follow the injection of relatively nonvirulent organisms into the limbs of animals. He attributed local tetanus to an ascent of toxin to the spinal cord, creating an arc of lowered threshold in the affected area. The toxins of more virulent infections were thought to be conveyed to the cord by the blood, affecting the shorter nerves supplying the muscles of mastication, the neck and the back. I assume that local tetanus developing after the prophylactic injection of antitoxin is the residuum of what would have been a virulent generalized infection had the preventive dose not been given. On the other hand, local tetanus occurring without prophylactic injection is probably the counterpart of the usually mild "experimental" tetanus. The following case and the previous case reported by me occurred in nonimmunized persons.

#### REPORT OF A CASE

T. S., a white sailor, aged 42, was admitted to the Anglo-American Hospital in Havana on Oct. 20, 1932. He complained of spasm of the right eye and difficulty in separating his teeth. Seventeen days before, he had cut his scalp against sea bottom while diving in the harbor at Kingston, Jamaica. The laceration had been sutured, but medical attention had not been sought since the day of the injury. Ten days later partial closure of the right eye was noted; this was followed by stiffness of the masseter muscles. On examination it was observed that the right palpebral fissure was narrowed by a spastic contraction which could not be relaxed and that the right corner of the mouth was slightly elevated. The incisor teeth could be separated about  $\frac{1}{4}$  inch (0.64 cm.). In the right frontal region was an encrusted, infected scalp wound, 8 cm. long, apparently healed by serum oozing from its lower end. The sutures were removed and a wet dressing applied. The temperature was 99 F. The tendon reflexes were not exaggerated, nor were there other significant physical findings or data from the history. There was no evidence of a present or preceding cellulitis of the scalp or forehead.

A presumptive diagnosis of local tetanus was made, and 5,000 units of antitoxin was administered intraspinally and 10,000 units intramuscularly. Both doses were repeated on the following day, and thereafter 5,000 units was given intramuscularly every six hours. The spinal fluid was normal cytologically and serologically. The roentgen appearance of the cranium was normal.

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7. Bruce, D.: Analysis of One Thousand Four Hundred and Fifty-Eight Cases of Tetanus, *J. Hyg.* **19:1** (July) 1920.

8. Ashurst, A. P. C.: Report on Tetanus, *Arch. Surg.* **1:407** (Nov.) 1920.

The patient's general and local condition remained unchanged. The wound on the scalp appeared to be uniformly healed. Because of the failure of the facial spasm and trismus to respond to treatment it was believed that the wound harbored tetanus bacilli. Accordingly on October 24 the wound was incised under local anesthesia. Beneath the pericranium of its anterior margin a collection of thin pus was encountered. The entire wound was swabbed with phenol, lightly packed and left open. Unfortunately no culture was made.

On October 28, both the facial spasm and the trismus were virtually abolished, the patient being able to open the affected eye widely (fig. 1 *B*). The dose of antitoxin was reduced to 10,000 units daily, and on November 1, its administration was discontinued and the patient discharged in satisfactory condition, with the wound on the scalp healing by second intention.

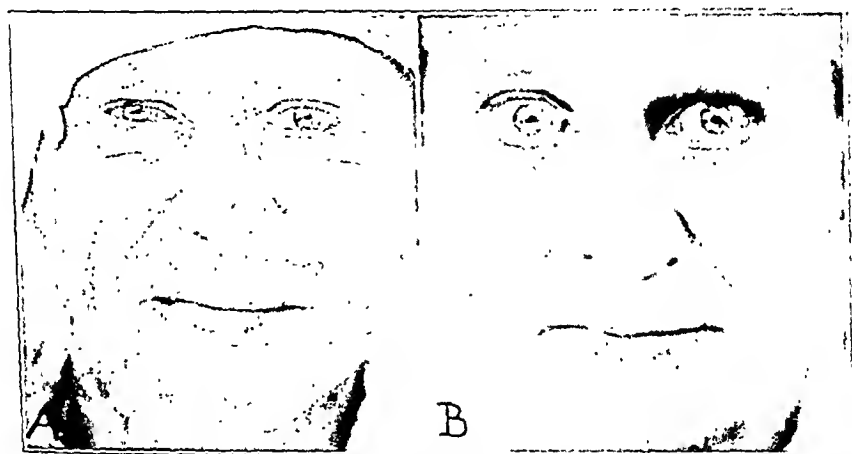


Fig. 1.— *A*, spasm of right orbicularis oculi seven days after onset, before the beginning of treatment. *B*, ability to relax orbicularis after completion of antitetanic serum therapy.

#### TREATMENT

In this instance, 10,000 units of antitoxin was given intrathecally and 180,000 units intramuscularly. It is probable that similar results could have been secured by the administration of a smaller quantity of antitoxin. However, the uncertain prognosis of cephalic tetanus indicated the large dosage. It is doubtful that cure would have resulted had the site of infection not been surgically exposed and phenolized; this fact emphasizes the value of phenol as originally stressed by Bacelli and recently by Bates.<sup>9</sup> The latter believed that 7,500 units intraspinally and a total of 40,000 units intramuscularly, given on the day of diagnosis, would suffice as well as larger doses. The problem of dosage remains unsettled, many observers believing that in severe cases of generalized tetanus cure has been effected by heroic doses (a total of

9. Bates, C. O.: Treatment of Traumatic Tetanus, *Am. J. Surg.* 18:58, 1932.



200,000 or more units). Not even these large quantities can be depended on to arrest the disease in all cases. Slimon,<sup>10</sup> for example, reported a case of cephalic tetanus with facial paralysis in which treatment was started on the day of initial symptoms. A total of 300,000 units was administered intravenously and intraspinally before a fatal outcome on the eighth day. In Grant's<sup>11</sup> case 160,000 units was employed, with recovery, in a patient aged 7 years.

#### INCIDENCE OF LOCAL TETANUS

In contrast to four cases reported before the World War, I have assembled reports of sixty-two cases recorded since 1921. Seventeen of these involved an extremity and forty-five, the head. An analysis of these cases is not attempted (see bibliography).

In general it may be said: that local tetanus is not exceedingly uncommon in civil practice; that it occurs with or without prophylactic inoculation, and that in peripheral cases the prognosis is fair, and in the cephalic type, guarded. In diagnosis, hysterical contractions and paralysis due to injury of cranial or peripheral nerves present the main difficulties. The case reported here showed tonic spasms of the right facial nerve distribution, with contracture of the orbicularis oculi and levator anguli oris. This phenomenon is in contrast to sluggish contracture of the upper eyelid observed by Danzer<sup>12</sup> in complete facial paralysis. It should be recalled that tetanic spasms may be intermittent or, as in this case, continuous and without relaxation. In addition, it is recognized that insufficiently treated local tetanus may become generalized. Andrewes<sup>13</sup> believed that in all local cases exhibiting trismus the patient should receive intraspinal treatment, whereas most writers are now in accord that all patients should receive at least one intrathecal injection. The most significant experimental investigation of local tetanus, that of Ransom,<sup>14</sup> pointed to the predominance of the direct action of tetanus toxin on muscle fibers in producing and maintaining contraction. Evidence was presented, however, which indicated that the action of toxin on the central nervous system played a minor but indispensable rôle in establishing the circuit of spasticity.

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10. Slimon, J. G.: Tetanus Complicated by Facial Paralysis, *Brit. M. J.* **2**:200 (July 30) 1932.

11. Grant, R. L. T.: Kopftetanus, *M. J. Australia* **2**:512 (Oct. 22) 1932.

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14. Ransom, S. W.: Local Tetanus: A Study of Muscle Tonus and Contracture, *Arch. Neurol. & Psychiat.* **20**:663 (Oct.) 1928.

## SUMMARY AND CONCLUSIONS

1. A case of local (cephalic) tetanus with recovery is recorded.
2. The comparative frequency of this condition is indicated by the large number of cases reported since the World War.

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# AN UNDIFFERENTIATED MÜLLERIAN DUCT IN A MAN

## AN UNUSUAL CONGENITAL ANOMALY AS A COMPLICATION OF AN INGUINAL HERNIA

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This case of a persistent müllerian duct is reported for its embryologic interest and rarity. That this anomaly occurs is now well known. However, this case merits recording, as only one identical case has appeared since, and to the best of my knowledge, none previously. While I cannot be dogmatic in my interpretation, I feel justified in the belief that this case showed the persistence of an undifferentiated müllerian duct in an adult male.

Several years ago this strange abnormality was encountered by the late Dr. Charles H. Peck in the course of a routine operation for a recurrent inguinal hernia at the Roosevelt Hospital. My interest was revived by the report of a similar case three years later by Dr. Randolph Matas, in the *Surgical Clinics of North America*.

Dr. Peck granted me permission to secure new pathologic sections from the original tissue. I discussed the sections with the late Dr. G. S. Huntington. He agreed with me that, judging by the position and histology, the anomaly might be a persistent müllerian duct. He did not feel, however, that the possibility of an accessory vas deferens could be ruled out, as he had encountered one some time previously. A drawing of the dissected specimen is appended. No other report of such a case could be found.

Several reported diagnoses of persistent müllerian ducts were proved to be erroneous. With one exception the structures were accessory ureters of an unusual type. Their retention under that title has resulted in much confusion in current literature as to the etiology of accessory ureters. This confusion is inexcusable in view of the excellent work done in this field, notably that of the late Dr. Huntington.

In the absence of other cases of persistent müllerian ducts of similar type, it is necessary to establish the possibility here formulated, briefly to review the subject of the persistence of the müllerian duct in the male in the lesser and more complete stages of differentiation.

### REPORT OF A CASE

An unmarried man, aged 32, entered the Roosevelt Hospital in April 1919, in the service of the late Dr. Charles H. Peck, for the repair of a right recurrent inguinal hernia.

The history was not noteworthy except for an attack of gonorrhea in 1908 and a previous operation at another hospital on Aug. 8, 1911, for right inguinal hernia and "acute hydrocele." He was discharged from that hospital as cured on September 12, with the history of a wound infection and swelling of the testicles.

The hospital records of this operation were scanty and inaccurate. The operative findings were described as "a double acute hydrocele with edematous

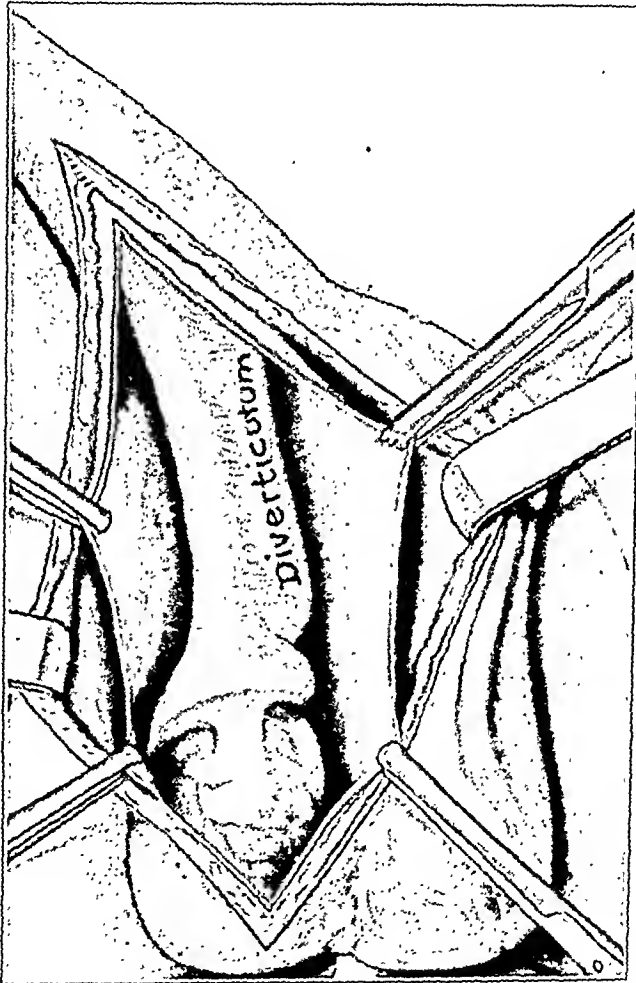


Fig. 1.—Except for the added length of the anomaly, this illustration from Dr. Matas' case would suffice for Dr. Peck's. "The 'diverticulum' is represented as it presented itself on opening the hernial sac, as a part of the spermatic cord in a congenital hernia." (Reproduced from *Surgical Clinics of North America* [2:1155, 1922].)

thickened tissues and a left hernia." Elsewhere the hernia was correctly described as right. The history mentioned a recent painful swelling of the testicles, and this condition was mentioned also in the report of the physical examination. The operative treatment of the hydrocele was not mentioned; the history suggested

an epididymitis. Whether true hydrocele was present or whether the malformation was present with the "edematous thickened tissues" must remain conjectural.

Examination on entrance to the Roosevelt Hospital showed the scar from the former operation over the right inguinal canal, an enlarged external ring and a



Fig. 2.—Low power photomicrograph showing cross-section of wall of duct. Note the large caliber of blood vessels, especially in the submucosa, and the thick muscular wall. The rectangle at the mucosal surface shows the site of the high power photomicrograph.

moderate-sized elastic mass, which descended into the scrotum when the patient coughed or strained. I found no other abnormality except scattered râles at the bases of the lungs, which were attributed to chronic bronchitis. No feminine characteristics were noted.

The patient was operated on on April 17, 1919, by Dr. Peck under nitrous oxide-ether anesthesia. A medium-sized sac was readily found; it was dissected free, transfixed, ligated and divided at the base. With considerable difficulty the vas and cord were dissected free and isolated from a large tubular structure. The vas was found to be severed at one point, the cut ends being separated about  $\frac{1}{2}$  inch (1.27 cm.) and buried in scar tissue. Further dissection revealed a normal pampiniform plexus and a large thickened, tubular structure, parallel to the other structures of the cord, ascending from the middle of the inguinal canal through the internal ring and palpated to the base of the bladder. This anomaly was carefully dissected from the other structures. It ended blindly at the distal end. Its diameter was about one-half inch and was uniform as far as it could be traced. It was thick-walled and hollow, and filled with a mucinous secretion, like the white of an egg. This structure could not be identified at



Fig. 3.—High power photomicrograph of the wall of the duct, showing the mucosa and submucosa. The epithelium and type of glands are seen in greater detail.

the time, but as it appeared to have contributed to the hernia and its recurrence, it was ligated and divided as high as possible, and the proximal stump was dropped back in the pelvis. The vas was left beneath the internal oblique muscle. The remaining structures of the cord were transplanted. The closure was made in the usual modified Bassini manner, with transplantation of the pampiniform plexus.

Except for considerable swelling of the right testis the patient's convalescence was uneventful, and he was discharged as cured in May 1919. Every effort to trace him after his discharge was futile.

The microscopic examination of this remarkable structure was extremely interesting. It proved to have an internal lining of mucous membrane. This consisted of high columnar epithelium, with an occasional simple, tubular, glandular arrangement. The glands extended a short distance into the basement mem-

brane, consisting of connective tissue in a network arrangement containing a few lymphoid cells and an occasional polymorphonuclear leukocyte. Beneath the mucosa was an arrangement of tissue in bundles running in various directions. This thick layer had undergone a marked hyaline degeneration, and from its arrangement was probably muscular. The mucosa was well supplied with blood vessels, and there were large vessels in the deeper layers.

#### MATAS' CASE

Matas' case is remarkably similar:

A man was operated on for hernia. He had had no previous operative intervention. The report of the operation is as follows<sup>1</sup>:

"The most interesting feature of the operation at this stage was the appearance of a long tubular mass which bulged prominently into the hernial sac and extended the full length of the spermatic cord. It began about one inch above the epididymis, extending upward as a component of the spermatic cord into the inguinal canal, and beyond the internal ring, thence backward and downward, following the course of the vas deferens to the base of the bladder, where it was apparently lost in the right seminal vesicle and prostate. It was entirely extra-peritoneal, but most intimately adherent to the posterior layer of the sac, which was extremely thin, making it difficult to detach it from the underlying components of the cord.

"This anomalous mass was first seen projecting through the thin translucent posterior layer of the sac, and had the appearance of a long narrow sausage. At first it was taken to be a chronically inflamed spermatic plexus, enlarged and indurated by thrombophlebitis. On further investigation and dissection the enlargement of the cord was found to be due to the presence of this anomalous structure or organ which could not be identified with any of the normal components of the cord. It was blended and fused most intimately with the vas deferens, and the vessels of the cord were displaced and bound together behind it. An incision was made longitudinally into it and parallel with its long axis. This at once opened a hollow tube which, beginning about one inch from the testicle, ran along the cord to the level of the internal ring where it disappeared in the retroperitoneal connective tissue. A no. 10 (English) soft rubber catheter was introduced into the lumen of the tube and it traveled easily and without resistance beyond the internal ring, a distance of seven or eight inches where it met with a resistance and would go no farther. No fluid or secretion of any sort escaped from the catheter when it was withdrawn, showing that the abnormal canal was not a diverticulum of the bladder as had been suggested. Only a long string of clear glairy mucus followed the extraction of the catheter.

"The extra-abdominal part of the diverticulum from its blind terminus in the scrotum up to the level of the internal ring was fully  $3\frac{1}{2}$  inches in length, about half the thickness of the little finger and formed a distinct, well-lined, glistening mucus canal of a bluish white color. The mucous canal easily admitted a

1. Matas, R.: A Rare Anomaly Found in a Congenital Right Inguinal Hernia; a Tubular Diverticulum or Prolongation of the Right Seminal Vesicle, Extending into the Scrotum as a Component of the Spermatic Cord, *S. Clin. North America* 2:1155, 1922.



no. 12 E. catheter, and was wrapped up in a thick, easily differentiated muscular coat covered by an areolar layer, which together gave the wall of the tube an even thickness of at least  $\frac{1}{4}$  inch. With the finger introduced into the peritoneal cavity through the hernial canal the outline of this tubular cord could be easily traced over the peritoneum and followed to the base of the bladder. The same

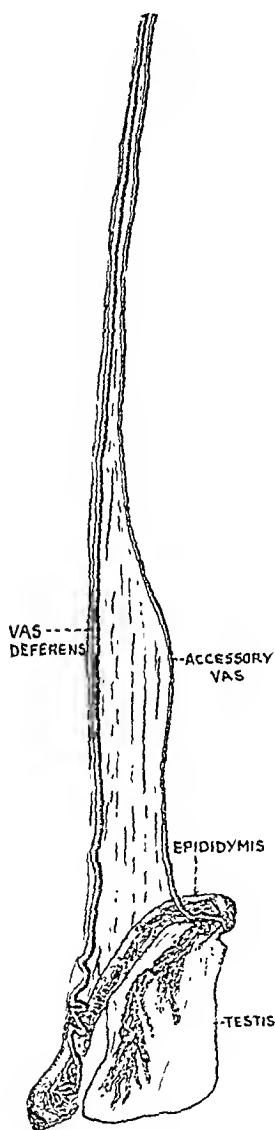


Figure 4

Fig. 4.—Accessory vas deferens into which injections of mercury have been made (illustration supplied by the Anatomical Museum of the Columbia University College of Physicians and Surgeons).

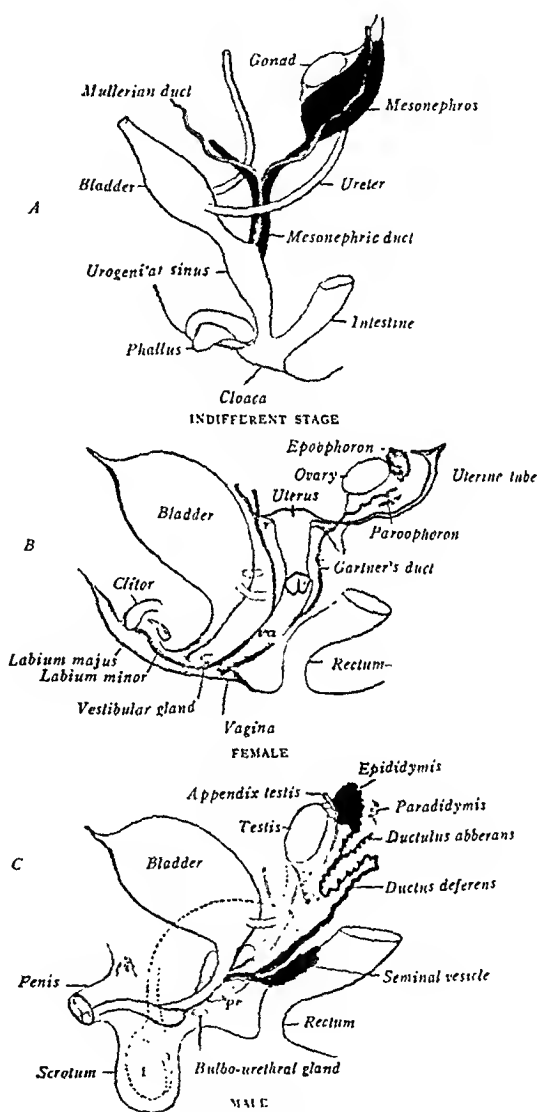


Figure 5

Fig. 5.—Müllerian and wolffian ducts.

impression was conveyed when the diverticulum with the attached vas deferens was followed as far as the finger could reach into the pelvis through the perivesical extraperitoneal space."

## COMMENT

Matas was unable to find a similar case in the literature. He concluded that the most likely explanation for the anomaly was that a seminal vesicle had been carried down through the inguinal canal with the descent of the testis. I requested a section for histologic study, but unfortunately, owing to a removal of the hospital, no slides or histologic report could be obtained.

Hypothetically, there appear five reasonable possibilities: (1) an anomaly due to a previous operation or hydrocele, (2) a diverticulum of the bladder, (3) a seminal vesicle, (4) an accessory vas deferens and (5) a persistent müllerian duct.

1. The large size of the anomaly and the identification of a normal vas in the operation rule out its artificial production by operative intervention or occlusion of the vas. The patient in Matas' case had not previously been operated on. It is impossible to conceive of a hydrocele of the cord giving a gross or microscopic picture such as that illustrated.

2. Diverticulum of the bladder may be excluded on the basis of the histology as well as the inability at the time of the operation to demonstrate a connection with the cavity of the bladder.

3. The seminal vesicle might descend with the testis, as was suggested by Matas in the discussion of his case. The histology, however, is somewhat different from that of a seminal vesicle, nor have I found a satisfactory basis for such an abnormality on embryologic or phylogenetic grounds. The seminal vesicles arise in the embryo as lateral diverticula budding from the caudal end of the wolffian ducts in the same location in which they are found in the later and final stages of development. At no time do they come into intimate contact with the testis. It is difficult to see how the descent of the testis could influence the position of the abnormality; nor is there any other developmental reason for its appearance in the inguinal canal.<sup>2</sup>

4. As is shown in the accompanying illustration (fig. 4), an accessory vas deferens might be present, branching off near the prostate and paralleling the vas. As far as can be determined, no such condition has been described in the literature, although this anomaly was known to the late Dr. Huntington, who dissected the specimen illustrated. He also possessed a corrosion specimen obtained from one of the lower animals of the lizard group, illustrating the phylogenetic

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2. (a) Huntington, G. S.: *The Genetic Interpretation and Surgical Significance of Some Variations of the Genito-Urinary Tract*, Harvey Lecture, Philadelphia, J. B. Lippincott Company, 1906-1907, p. 235. (b) Keibel, F., and Mall, F. P.: *Manual of Human Embryology*, Philadelphia, J. B. Lippincott Company, 1910-1912.

grounds for this anomaly. He had encountered several cases in the dissecting room. The extreme rarity of the anomaly is probably due more to the failure to search for it than to its infrequent occurrence. It is a condition to bear in mind in operations for sterilization, or in injury or disease of the vas deferens. On examining the slide, Dr. Huntington did not feel that there was sufficient evidence for excluding this possibility or that of a persistent müllerian duct. It is perhaps worth noting that the accessory vas illustrated is smaller than the normal vas, whereas the anomaly is much larger.

5. One hypothesis is left, which I believe to be the most probable explanation for this unusual structure, namely, a persistent müllerian duct, although I concede the remote possibility discussed in the preceding paragraph. One is immediately struck by the similarity of the epithelium of the structure to that lining the uterus and tubes. The glandular arrangement is similar to that of the fundus uteri. The large blood vessels and thick muscular coat also support the analogy. The hyaline degeneration strengthens the belief that this is a rudimentary or nonfunctioning organ. Its anatomic position is also in accordance with this hypothesis.

Its location and relationship correspond with the present knowledge of the development of the müllerian duct. It is generally acknowledged by embryologists that the nonpedunculated hydatid which is found near the upper pole of the testis represents the remnant of the cephalic end of the müllerian duct, while the utriculus prostaticus located near the middle of the posterior surface of the prostate represents the caudal end of the müllerian duct in the male. Assuming its persistence, it would follow that the descent of the testis would carry the duct into the position occupied by the anomaly. An analogous condition in the female is that of an indirect inguinal hernia in which the ovary has descended through the enlarged canal of Nuck into the labia majora, carrying the cephalic end of the tube with it. The tube in such a case represents the differentiated müllerian duct.

Eight cases were found in the literature under the title of persistent müllerian ducts. Investigation reduced these to six: (1) Boogard's,<sup>3</sup> 1876, which was described by Pouchet;<sup>4</sup> (2) Barth's,<sup>5</sup>

3. Boogard, J. A.: *Persistencie der Müllersche gangen bij een wassen man*, Verhandl. d. k. Akad. v. Wetenschap, Amsterdam 9:266, 1876.

4. Pouchet, G.: *Persistence du canal de Müller chez l'homme adulte*, J. d'anat. et de physiol 13:200, 1877.

5. Barth, M.: *Anomalie de développement de l'utricule prostatique; persistance de l'organ de Müller du côté droit, en forme de poche diverticulaire passant sous la vessie; soulèvement de la muqueuse vésicale formant valvule (retention d'urine; dilation consécutive des uretères et hydronéphrose double)*, Bull. Soc. anat. 53:483, 1878.

1879, the subject of papers by Rémy<sup>6</sup> and Moutard-Martin<sup>7</sup>; (3) Ord's,<sup>8</sup> 1879; (4) Reliquet's,<sup>9</sup> 1887; (5) Nicolich's,<sup>10</sup> 1905, and (6) Martin's,<sup>11</sup> 1878. The first five can be discussed under the same head, as they are similar except for unessential details. All were found at autopsy and all were in males from childhood to middle age. Some were bilateral, and others unilateral. In every case the ducts arise from a body situated above the upper pole of the kidney; they parallel the ureter and are attached below the ureteral orifice and bladder in the region of the verumontanum of the urethra, a definite communication being noted in some of the cases with the urethra at this point. This anomaly resulted in an obstruction near the neck of the bladder which caused hydronephrosis and uremia and which was the direct cause of death. No microscopic studies were reported of any of these cases. Boogard noted that the upper end of the canals had remained in relation with the kidneys and had not followed the testicles in their migration.<sup>3</sup> Pouchet<sup>4</sup> and Rémy<sup>6</sup> argued from that that the nonpedunculated hydatid was not a remnant of the müllerian duct. Rémy<sup>6</sup> had found the hydatid in its usual position on the testis on the same side as the duct in the case of Barth. The verdict of time, however, has preserved the origin of the nonpedunculated hydatid. Pouchet's argument that these ducts could not be ureters because they were not connected with the kidneys and emptied into the urethra has likewise been proved erroneous. Ord noted that the body above the kidney "had the structure of a renal organ with evidence of contraction and degeneration."<sup>8</sup> Reliquet at first considered his case to be one of an accessory ureter, but was led to reverse this belief by Duval, who was familiar with the case of Barth.<sup>5</sup> One is immediately struck by the similarity to a rare but well known type of accessory ureter with an accessory kidney to which they conform in every respect. The embryologic basis for this type of ureter was explained by the late Dr. Huntington in the Harvey Lecture of 1906, delivered at the

6. Rémy, C.: Sur l'utricule prostatique et les canaux de Müller chez l'homme, *J. d'anat. et de physiol.* 15:175, 1879.

7. Moutard-Martin, R.: Cas de persistance du conduit de Müller avec anomalie de développement de l'utricule prostatique chez un enfant de six ans, *Bull. Soc. anat. de Paris* 54:529, 1879.

8. Ord, W. M.: Malformation of the Genital Organs of a Man with Persistence of One of the Ducts of Müller, *M. Times & Gaz.*, London 2:654, 1879.

9. Reliquet: Persistance du canal de Müller. Hydronephrose du rein et de l'uretère droit. Pyelonéphrite calculeuse du rein gauche très hypertrophie, *Progrès med.* 5:205 and 230, 1887.

10. Nicolich, G.: Persistance de conduit de Müller, *Assoc. franç. d'urolog.* Proc. verb. 8:580, 1905.

11. Martin, E.: Mémoire sur un cas de persistance des canaux de Müller, *J. d'anat. et de physiol.* 14:21, 1878.

New York Academy of Medicine. He described it as a complete reduplication of the ureter and vesical termination of one duct, while the other duct empties, in association with the ejaculatory duct, into the prostatic urethra.<sup>2a</sup> The case of Nicolich, the last to be reported, was presented before the Association française d'urologie in 1905. Dr. J. Albarran, who was present, objected to the diagnosis of Nicolich, pointing out in the gross specimen the similarity of the duct to the ureter; the cortex of the accessory kidney, which Nicolich had believed to be a congenital gland, presumably an ovary. It is also significant that no similar cases have been reported as showing persistence of the müllerian duct since that time. On these grounds I feel justified in denying the authenticity of these cases as instances of müllerian ducts.

The case reported by Martin was that of a 7 or 8 month fetus, with an enormously distended bladder, no trace of urachus or urethra, an imperforate anus, no vaginal canal or genital glands and two tubes running from the region of the kidneys to the bladder, parallel and internal to the ureters.<sup>11</sup> The undeveloped external genitalia were suggestive of the female. If one accepts the assumption that these tubes are müllerian ducts, one would also be justified in assuming that this was a female fetus, as otherwise it was entirely sexless. In any case, the monstrosity does not come within the confines of this paper.

In the absence of identical cases, it becomes necessary briefly to review the question of hermaphroditism.

It will be recalled that at an early stage of fetal life every person is potentially bisexual. The primitive genital glands of both sexes arise in the genital ridge. Two tubular structures appear on both sides—the wolffian duct and the müllerian duct. In the male the gland at an early stage develops into the testis. The vas deferens, the seminal vesicles and the epididymis are formed from the wolffian duct. Normally the müllerian duct atrophies and leaves only vestigial remains, namely, the canals of Rathke, the nonpedunculated hydatid and the prostatic utricle. The nonpedunculated hydatid, when present, is found on the testicle and represents the remains of the cephalic end of the müllerian duct; the prostatic utricle near the center of the posterior surface of the prostate represents the caudal end.<sup>2b</sup>

In the female the müllerian ducts of the two sides fuse at the lower end and eventually form the upper part of the vagina, cervix, corpus uteri and fallopian tubes. The remnants of the wolffian ducts are represented by the canals of Gartner, the longitudinal canal of the organ of Rosenmüller and the hydatid of Morgagni.<sup>2b</sup>

Hermaphroditism is a subject of myths and early art of almost all races from the earliest times. The early reported cases were bitterly contested, and every possible and some impossible objections were voiced against any one so rash as to report a case. In 1896 Blacker

and Lawrence<sup>12</sup> reported a case and reviewed twenty-eight cases, of which they considered Heppner's bilateral case, and Obolensky's and Schmorl's unilateral cases and their own case as proved. Blacker and Lawrence's slides were reviewed by two eminent pathologists, who agreed that the patient was not a hermaphrodite, but, paradoxically, one claimed that it was undeniably a female, while the other considered that it was a male. To Simon must go the credit for placing the diagnosis on an indisputable footing and ending the controversy for all time. He reported a case of Gané and reviewed the cases of Salen and of Blacker and Lawrence, which he accepted without reservation; the three cases mentioned earlier were acceptable to him with some reservations.<sup>13</sup> Since Simon's report many more cases have been added.

True hermaphroditism in the sense of functional glands of both sexes with accessory organs has never been reported in any vertebrate, although it is not uncommon in the lower forms of animal life. There is some unknown controlling factor which prevents the coincidental development of functioning glands of both sexes in a single person. One might apply the old definition of a poison to hermaphroditism: Every one or no one is a hermaphrodite, it being a question of degree.

The so-called true hermaphroditism of Klebs<sup>14</sup> is based on the findings of glands of both sexes, identifiable microscopically and morphologically, in one person. These glands may be bilateral or unilateral, or the two may be incorporated together in an ovotestis. The ovotestis is interesting surgically from the occasional tumors arising in the non-functioning gland.

In addition to the glandular hermaphrodites, many cases are reported of tubular hermaphrodites. For example, a person may have the glands of one sex and at the same time bear the tubular accessory structures of both sexes. These persons are usually termed tubular pseudohermaphrodites. Obviously, the glandular and tubular hermaphrodites may be combined, which gives the nearest approach to an actual hermaphrodite. Even in these combined cases the sex may be determined, if one can ascertain which of the glands are functioning.

The pseudohermaphrodites again vary from the completely differentiated structures of the opposite sex to an approach to the vestigial remains which are normally found in most persons.

12. Blacker, G. F., and Lawrence, T. W. P.: A Case of True Unilateral Hermaphroditism with Ovotestis Occurring in Man, with Summary and Criticism of the Recorded Cases of True Hermaphroditism, *Tr. Obst. Soc. London*, 1896, 38: 265, 1897.

13. Simon, W.: Hermaphroditismus versus, *Virchows Arch. f. path. Anat.* 172:1, 1903.

14. Klebs, E.: *Handbuch der pathologischen Anatomie*, Berlin, A. Hirschwald, 1873.

I shall limit the consideration to the male pseudohermaphrodite with the persistent müllerian duct. The cases reported by Simon and many others since that time have shown that an ovary and the completely differentiated müllerian duct may exist in an otherwise normal male. Many cases have been reported of males with persistence of the müllerian duct in the completely differentiated state without ovarian tissue. This has been described as a predisposing cause of hernia. Many of these cases were discovered through the finding of these derivatives in a hernial sac.

Duse<sup>15</sup> collected fifteen cases of masculine pseudohermaphrodites with persistent differentiated müllerian ducts associated with hernias, and LaHaye added seven more in 1920, with an interesting résumé on the subject of hermaphroditism.<sup>16</sup>

There is a wide gap between this condition and the condition which has been described as an enlargement of the prostatic utricle. These vary from a scarcely perceptible enlargement of the utricle to a condition in which one or two small, short tubes or solid strands of tissue arise from the enlarged utricle. A case reported by Young and Cash is representative of this group.<sup>17</sup>

I believe that Dr. Peck's and Dr. Matas' cases are an intermediate and connecting link between the two types of male pseudohermaphrodites described earlier. In the lower animals a similar condition has been reported in moles, beavers and frogs.<sup>16</sup> I prefer the term "persistence of the undifferentiated müllerian duct in a male" to distinguish such cases as ours from the other types of persistence, as they form a distinct clinical entity.

It would be expected that cases such as ours would occur numerically in an intermediate position between the instances of differentiated müllerian duct and the cases of enlargement of the prostatic utricle, as these approach the normal state. I can account for the disparity of reported cases only on the basis that practically all of the male pseudohermaphrodites with the differentiated female accessory structures are reported, owing to the easy recognition of the condition and its dramatic possibilities, and that cases like ours are not reported. If my diagnosis is correct, I should expect that more cases will be reported in the future. There is nothing in the histologic picture which would not fit this hypothesis.

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15. Duse, A.: *Utero masculino erniáto con distopia transversa del testículo sinistro*, Clin. chir. **18**:1597, 1910.

16. LaHaye, P.: *Reflexions au sujet d'un cas d'hermaphroditisme tubulaire masculine interne*, Thèses de Paris, 1919-1920, p. 29.

17. Young, H. H., and Cash, J. R.: *A Case of Pseudo Hermaphroditismus Masculinus, Showing Hypospadias, Greatly Enlarged Utricle, Abdominal Testis, and Absence of Seminal Vesicles*, J. Urol. **5**:405 (May) 1921.

As both of the cases described were discovered in the course of repair of hernias, hernia seems to be a predisposing factor in the causation of the anomaly. It is also interesting to note that the treatment adopted by two master surgeons was the same, although neither had seen a similar condition. The recurrence in our case was probably due to the failure to excise the anomalous structure at the first operation.

#### CONCLUSIONS

1. The cases described I believe to be instances of undifferentiated persistent müllerian ducts in adult males, though I admit the remote possibility that the anomalies are accessory vasa deferentia.
2. The cases reported to show persistent müllerian ducts, with one exception, proved to be cases of accessory ureters and accessory kidneys.
3. This condition is a predisposing cause of hernia.
4. The proper treatment, if these anomalies occur with hernia, is excision to prevent recurrence.
5. A link is added between the enlarged prostatic utricle and the differentiated müllerian duct.
6. A case of an accessory vas deferens is cited with illustration.

NOTE.—The late Dr. Charles H. Peck permitted me to report this case, and Dr. James I. Russell renewed this consent. The late Dr. George S. Huntington assisted in the investigation, and Dr. A. R. Stout reviewed the histology. Mr. Frederick Kraus made the translation from the German.



# ANOMALIES OF INTESTINAL ROTATION AS A CAUSE OF INTESTINAL OBSTRUCTION

REPORT OF TWO PERSONAL OBSERVATIONS; REVIEW OF ONE  
HUNDRED AND THREE REPORTED CASES

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AND

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DURHAM, N. C.

In the practice of abdominal surgery a clear conception of the various possibilities of derangement of intestinal rotation and fixation is essential. Anomalies in position of the intestinal tract may exist without symptom and manifest themselves incidentally at operation. Because of the bewildering disposition of the viscera the operation may be unnecessarily prolonged or the ultimate object abandoned. Under other conditions, because of the abnormal position of the cecum, a patient with acute appendicitis may be watched until perforation has occurred. Of greater importance to the surgeon, however, are the forms of intestinal obstruction secondary to torsion or kink, dependent on abnormalities of intestinal rotation and fixation. Since many of these obstructions are chronic and date from birth, and since the surgeon usually sees the patient only in consultation, it is equally important for the internist and the pediatrician to be familiar with this characteristic clinical picture.

The occurrence in our practice within one month of 2 cases of volvulus of the entire mesentery secondary to anomalies of intestinal rotation and fixation and the appearance of frequent reports of similar cases in the literature of recent years make it evident that the condition is more frequent than is generally accepted. It is the purpose in this report (1) to review the stages in normal intestinal rotation and the possibilities of abnormality in each, (2) to present our 2 cases and (3) to review the literature on anomalies of intestinal rotation as a cause for the development of acute and chronic intestinal obstruction.

## EMBRYOLOGIC DEVELOPMENT

Although much of the embryologic development of the intestinal tract was known and described as early as 1817 by Meckel<sup>1</sup> most of our present knowledge of intestinal rotation dates from the work of

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*From the Department of Surgery, Duke University School of Medicine.*

1. Meckel, J. F.: *Blindungsgeschichte des Darmkanals der Säugetiere und namentlich der Menschen*, Deutsche Arch. f. Physiol. 3:1, 1817.

Mall<sup>2</sup> in 1898 and of Frazer and Robbins<sup>3</sup> in 1915. We have drawn freely from the latter two sources and from Dott's<sup>4</sup> masterful article published in 1923.

At the end of the fifth week of intra-uterine life the abdominal portion of the intestinal tract may be schematically represented as in figure 1. The entire alimentary tract is suspended in the midline by a common dorsal mesentery. The tract is divided into three parts according to form and blood supply: the foregut forming the upper loop supplied by the celiac axis, the midgut forming the umbilical loop supplied by the superior mesenteric artery and the hindgut or lower loop supplied by the inferior mesenteric artery. The midgut grows rapidly, and by the end of the fourth week the vitello-intestinal duct has lost its connection with the yolk sac and umbilical cord. Available intra-abdominal space is so diminished by the rapid growth of the liver and the midgut loop that the latter is extruded into the root of the umbilical cord as a temporary and physiologic umbilical hernia. At the fifth week the midgut loop still lies in the sagittal plane, the apex of the loop being represented by the remnant of the vitelline duct and the termination of the superior mesenteric artery. The anterior segment of this loop is termed the prearterial segment, and the posterior, the postarterial segment.

At an early period the lower end of the foregut and the upper end of the hindgut become fixed points from which the midgut loop is suspended. The upper part of the duodenum is deviated to the right by the bulging and unequal growth of the greater curvature of the stomach. It becomes fixed in this location by the thickening and shortening of its mesentery and by the outgrowth of the pancreatic rudiment. From the upper end of the hindgut a retention band passes upward as a thickening in the mesentery to the region of origin of the superior mesenteric artery. This band does not keep pace in growth with the gut or remainder of the mesentery and thus fixes the intestine at the junction of the midgut and hindgut. These two fixed points are close together, and the growth of the embryo causes their further approximation. The narrow isthmus which they form and from which the midgut loop hangs is called the duodenocolic isthmus. This early fixation of foregut and hindgut loops precludes the possibility of either loop taking part in intestinal rotation which is entirely confined to the midgut. Errors in disposition of the foregut or of the hindgut are rare.

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2. Mall, F. P.: Development of the Human Intestine and Its Position in the Adult, *Bull. Johns Hopkins Hosp.* 9:197, 1898.

3. Frazer, J. E., and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man, *J. Anat. & Physiol.* 50:75, 1915.

4. Dott, N. M.: Anomalies of Intestinal Rotation: Their Embryological and Surgical Aspects, with Report of Five Cases, *Brit. J. Surg.* 11:251, 1923.

The process of intestinal rotation is divided by Frazer and Robbins<sup>3</sup> into three stages. The first includes the time during which the midgut loop occupies the umbilical hernia and until it is returned to the abdominal cavity at about the tenth week. The second stage occupies the time during which rotation and reduction of the midgut into the abdominal cavity take place and is completed when the cecum reaches the right loin in the eleventh week. The third stage extends from this

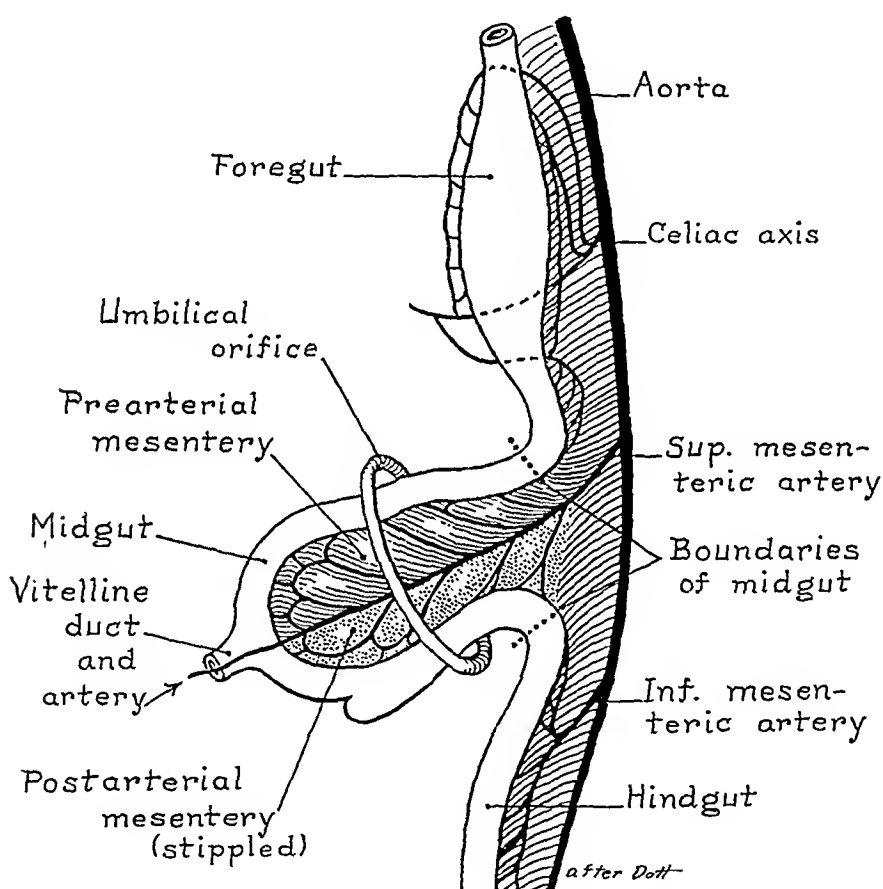


Fig. 1.—Diagram of the alimentary tract at the fifth week of intra-uterine life (lateral view). The foregut, midgut and hindgut are shown with their individual blood supply supported by the common dorsal mesentery in the sagittal plane. The midgut loop has been extruded into the umbilical cord.

time until shortly after birth. It is characterized by descent of the cecum and by fixation of the cecum and lower part of the duodenum by fusion of their mesenteries with the posterior parietal peritoneum. The first stage may be considered as a preparation for, and the third as the completion of, the important second stage during which in an exceedingly short time the reduction and major rotation of the intestinal tract occur.

*First Stage of Rotation.*—The essential feature of the first stage of rotation is the turning of the intra-umbilical loop from the sagittal to the horizontal plane so that the prearterial segment lies to the right and the postarterial segment to the left (fig. 2). This is brought about by the enlargement and down-growth of the liver carrying with it the left umbilical vein which depresses the proximal part of the prearterial segment.

Failure of the intestine to rotate beyond the first stage is seen in exomphalos, in which condition the embryonic hernia into the root of the umbilical cord persists in part or in full until birth. In this condition

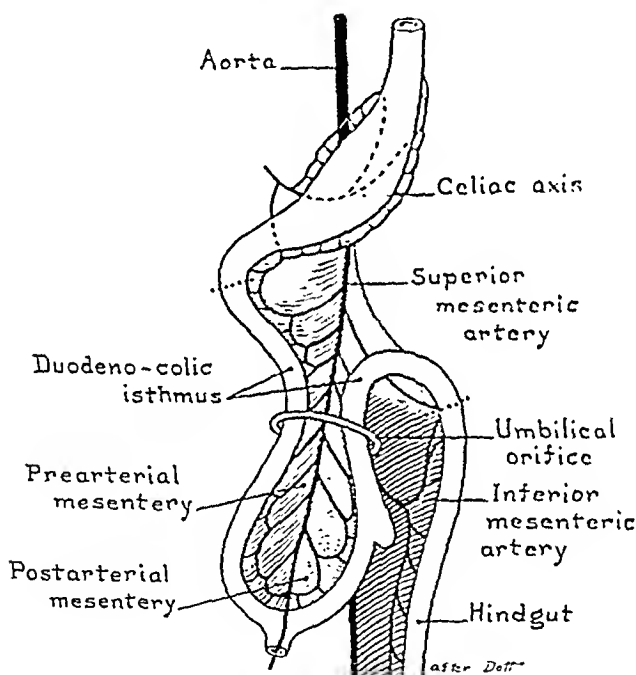


Fig. 2.—Diagram of the alimentary tract at the eighth week of intra-uterine life (anteroposterior view). The first stage of rotation is being completed. Note the narrow duodenocolic isthmus from which the midgut loop depends and the right-sided position of the small intestine and left-sided position of the colon. Maintenance of this position within the abdomen after birth is spoken of as non-rotation.

the hernia is covered by the thin and translucent umbilical cord, in contrast to the covering of skin in the usual umbilical hernia. The sac contains the nonrotated midgut loop occupying a position similar to that found in the embryo at the eighth or ninth week.

*Second Stage of Rotation.*—This is the stage of reduction and of major rotation of the midgut loop which takes place at the beginning of the tenth week and ends when the cecum reaches the right loin (figs.

3 and 4). This, the most important phase of the process of rotation, occurs quickly, and in none of the specimens studied by Mall or by Frazer and Robbins was the gut found in the process of its return. Frazer and Robbins pointed out that it is not possible for the gut to be returned en masse and that the cecum especially offers resistance to this passage. The proximal limb of the prearterial segment is thought to be reduced first, its coils entering the abdomen in an orderly sequence

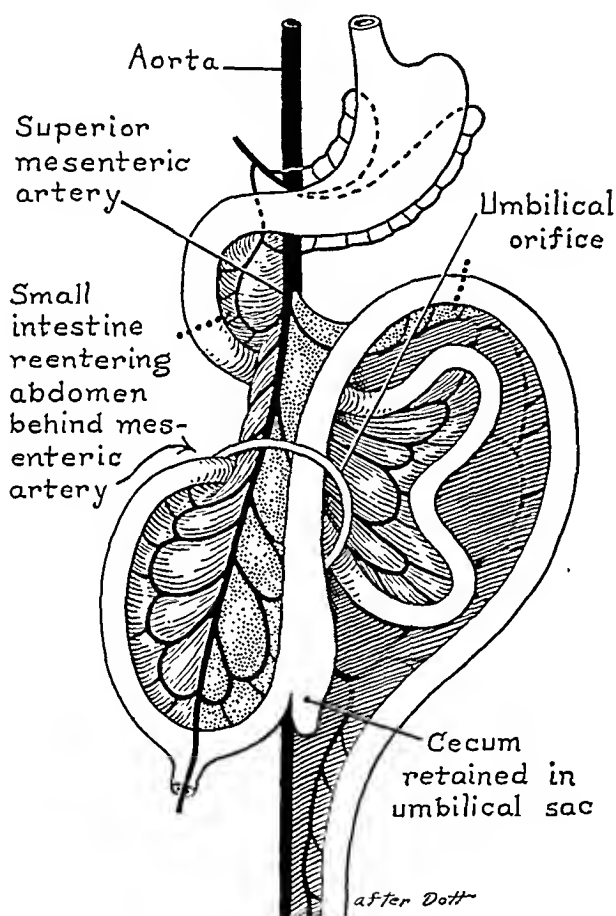


Fig. 3.—Diagram of the alimentary tract at about the tenth week during the second stage of rotation (anteroposterior view). The bowel in the temporary umbilical hernia is in the process of reduction, the most proximal part of the prearterial segment entering the abdomen to the right of the superior mesenteric artery first, and the remainder of the bowel following in orderly sequence. The superior mesenteric artery is held forward close to the abdominal wall by the cecum and ascending colon, permitting the bowel to pass under it. As the coils of small intestine collect within the abdomen the hindgut is displaced to the left and upward.

to the right of the superior mesenteric artery. As these coils collect within the abdominal cavity, the hindgut and its mesentery, which lie in the midline, are displaced to the left, backward and upward. The

splenic flexure and descending colon are thus carried into their normal position (fig. 3). The cecum and adjacent colon are reduced last. As they enter the abdomen and the colon straightens itself out they are deflected to the right (fig. 4). The final result of the second stage is seen to be a contraclockwise rotation of the midgut loop about the

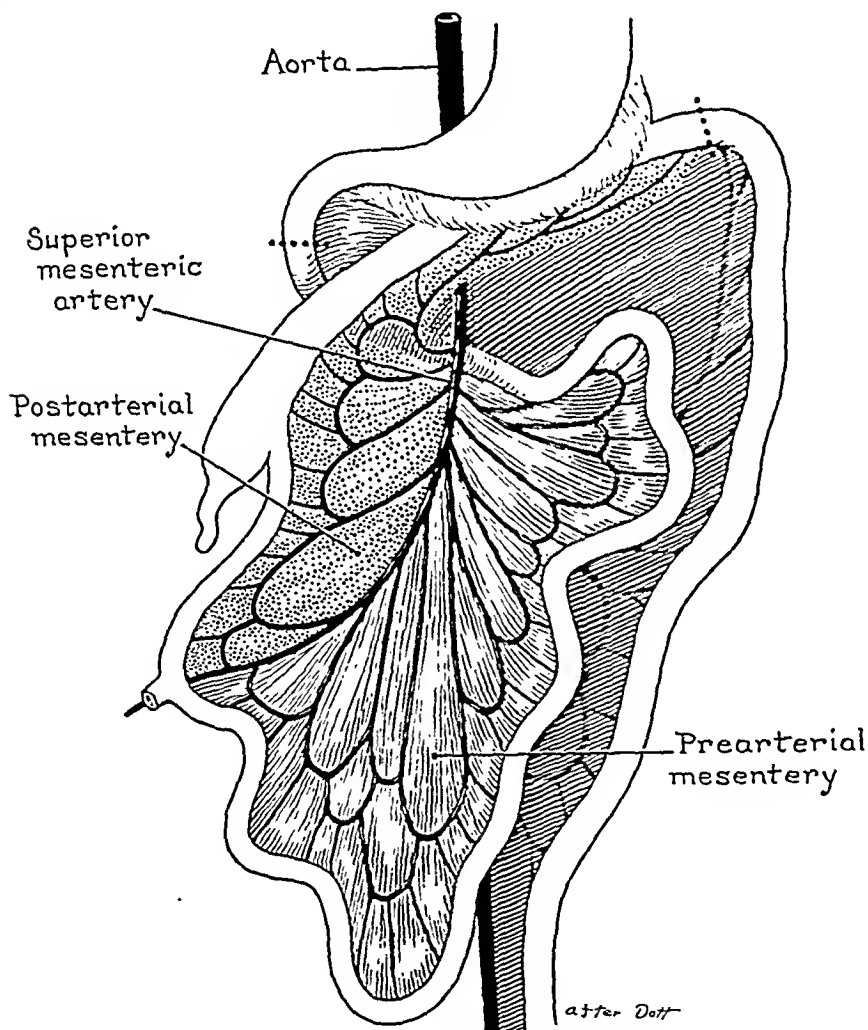


Fig. 4.—Diagram showing the condition of the alimentary tract at the end of the second stage of rotation (eleventh week). From its original sagittal position the midgut has rotated 270 degrees in a contraclockwise direction about the origin of the superior mesenteric artery. The essentials of the permanent disposition of the viscera have been attained.

axis of the superior mesenteric artery of 270 degrees from the sagittal position of the primitive umbilical loop. In this way the intestinal tract comes to occupy its position as normally seen in the adult, the duodenum

being placed behind the origin of the superior mesenteric artery while the transverse colon crosses the same point anteriorly.

Dott<sup>4</sup> classifies derangements of the second stage of rotation as nonrotation, malrotation and reversed rotation.

*Nonrotation.*—In nonrotation of the midgut loop (figs. 5, 6 and 7) the intestinal tract occupies a position within the abdomen fundamentally the same as in the embryo at the eighth week (fig. 2). The small intestine lies to the right of the midline and the colon to the left. The duodenum descends to the right of the superior mesenteric artery and is mobile

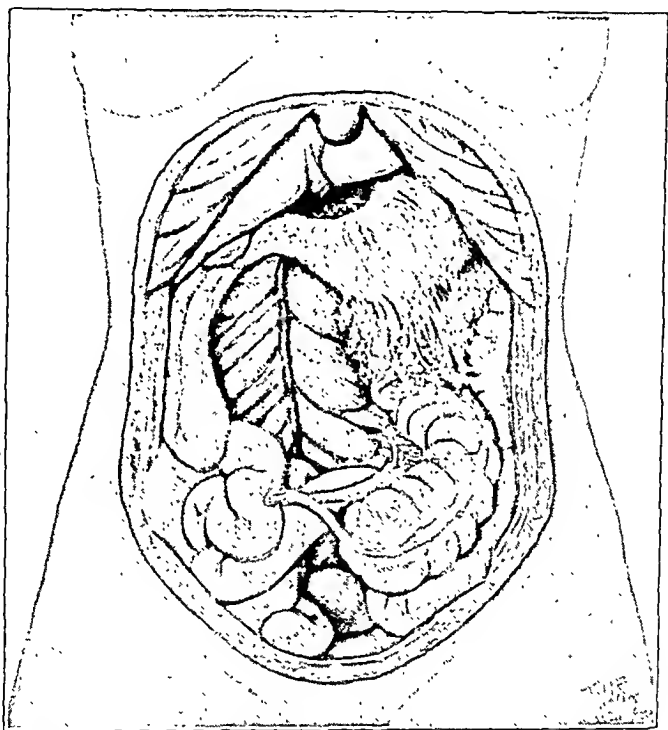


Fig. 5.—Disposition of the intestinal tract as found in nonrotation in the adult. The duodenum remains suspended on its mesentery and occupies a position entirely to the right of the vertebral column. The small bowel occupies the right side of the abdomen and the colon the left, so-called "left-sided colon." The terminal ileum crosses the midline to enter the cecum on its right side. Often a narrow U-shaped loop of transverse colon hangs between the ascending and the descending colon. The entire midgut is suspended on a common mesentery from the narrow duodenocolic isthmus at the origin of the superior mesenteric artery.

on its mesentery. The terminal ileum crosses the midline to reach the "left-sided" colon where it enters the cecum from the right instead of from the left. From this point the ascending colon passes upward on the left of the midline to a point behind the greater curvature of the stomach. Between this point and the splenic flexure is a narrow



Fig. 6.—Nonrotation as seen by roentgen examination of the barium-filled stomach, duodenum and small intestine in a woman aged 63 seen in consultation with Dr. J. M. Ruffin. The anomaly had caused no symptoms. The location of the duodenum and small intestine entirely on the right side of the vertebral column is shown.



Fig. 7.—Same patient as in figure 6. The barium-filled colon is seen entirely on the left side of the abdomen.



U-shaped loop of transverse colon. In this position there may be no secondary fixation of the mesentery, the entire midgut loop hanging free from the narrow duodenocolic isthmus (fig. 2). Such an arrangement predisposes to the development of a volvulus of the entire midgut loop. This occurred in 23 of the cases reviewed.

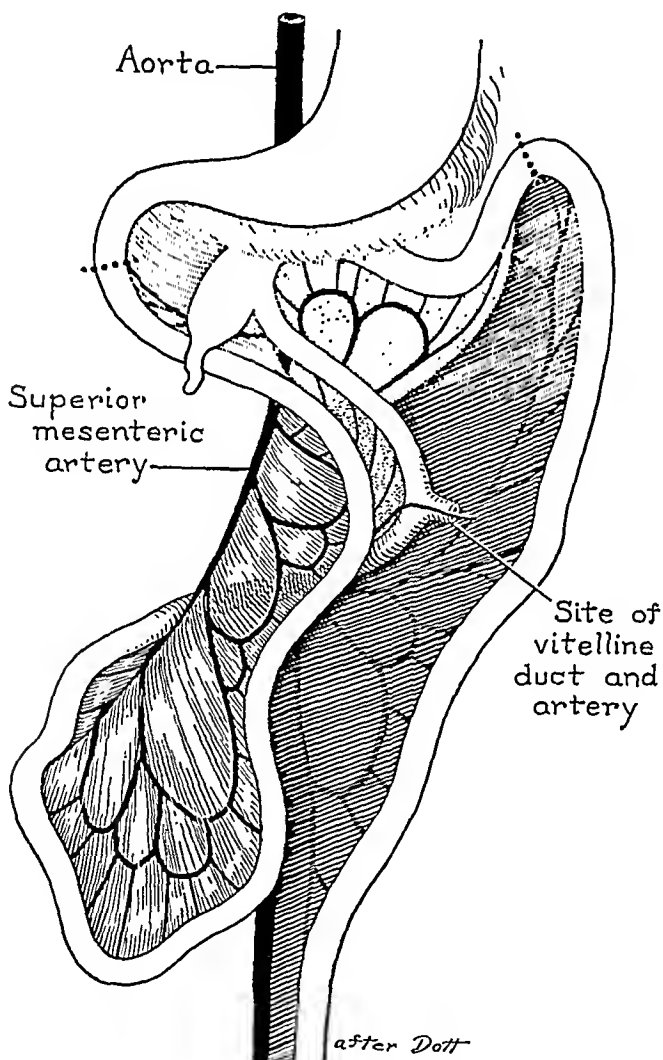


Fig. 8.—Diagram of the alimentary tract in one form of malrotation (antero-posterior view). The prearterial segment has gone through a reversed rotation (clockwise) of 90 degrees, while the rotation of the postarterial segment is arrested.

*Malrotation.*—By this term Dott designates the irregular defects of rotation and fixation. In one type the prearterial segment is reduced in front of the superior mesenteric artery while the rotation of the postarterial segment is arrested (fig. 8). In another type the prearterial segment has remained entirely on the right side, as in nonrotation, while the postarterial segment has rotated normally but has been prevented

from becoming fixed to the posterior abdominal wall by the presence of the unrotated small intestine. In both of these conditions the cecum and ascending colon retain their primitive mesentery in common with that of the small intestine (*mesenterium commune*). The attachment of the root of the mesentery to the abdominal wall is very short, and volvulus of the common mesentery may be produced. It is quite possible that with the abnormal mesenteric fixations which accompany these malrotations the intestinal lumen may be constricted. Seven cases have

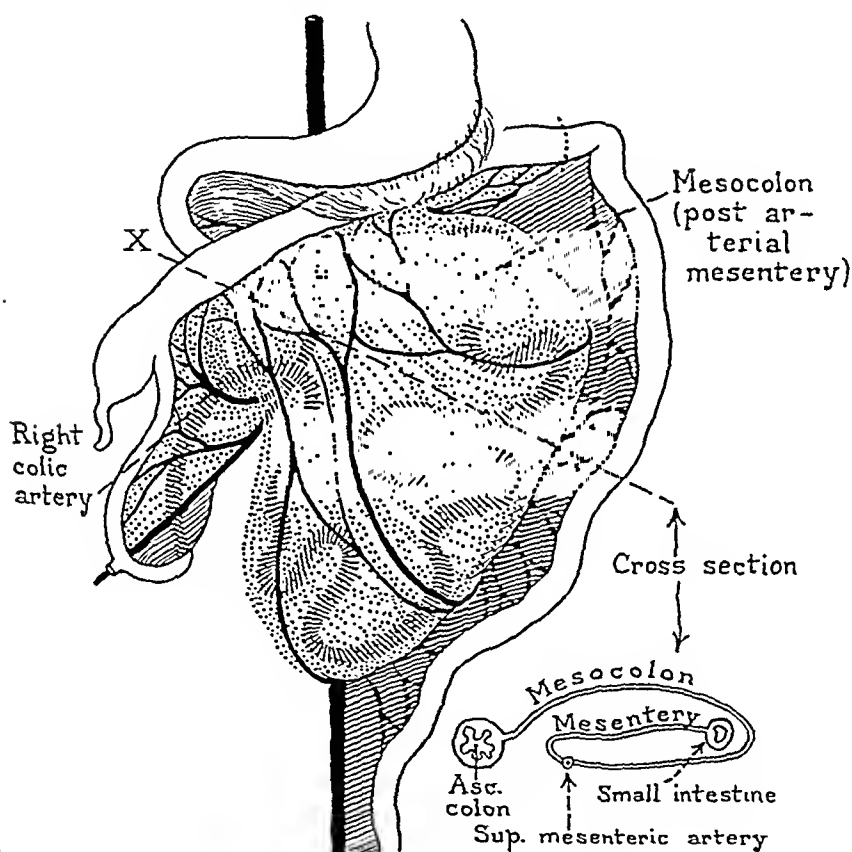


Fig. 9.—Diagram of a form of malrotation in which the small intestine rotates into the mesentery of the postarterial segment between the superior mesenteric artery and the colon (anteroposterior view). The small bowel is thus enclosed entirely in an envelop of peritoneum (after Haymond and Dragstedt).

been observed (table 3) in which there was some obstruction to the duodenum because of such an abnormality.

Another form of malrotation is that in which a massive intra-abdominal hernia is simulated by rotation of the prearterial loop into the mesentery of the postarterial segment between the superior mesenteric artery and the colon. Almost the entire small intestine may be contained in a peritoneal envelop thus formed (fig. 9). Such a con-

dition reported by Haymond and Dragstedt<sup>5</sup> existed without symptoms and was found in a man aged 67, who died of carcinoma of the stomach. Lickley and Cameron<sup>6</sup> reported an almost similar case without symptoms.

*Reversed Rotation.*—In this condition a 90 degree clockwise rotation takes place instead of the normal 270 degree contraclockwise one. Thus the transverse colon passes dorsally to the duodenum and superior mesenteric artery (fig. 10). If the normal fixation of the root of the mesentery toward the right iliac fossa takes place in this position the transverse colon becomes trapped in a tunnel beneath this acquired attachment. Fixation of the cecum and ascending colon is usually incomplete, and torsion of the mobile right half of the colon with obstruction

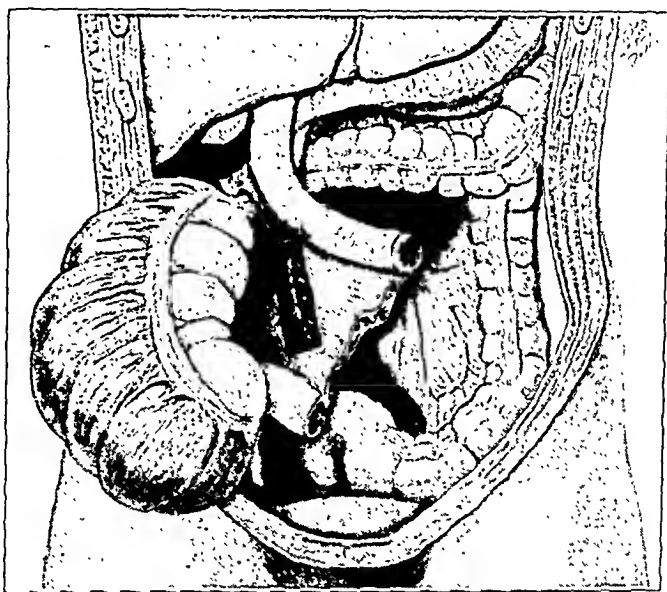


Fig. 10.—Drawing showing the conditions found in reversed rotation. The midgut has rotated 90 degrees in a clockwise direction, throwing the transverse colon under the duodenum. As the root of the mesentery becomes fixed the colon is trapped in a tunnel. The ascending colon retains its primitive mesentery, and in this case was obstructed by torsion at the point where it entered the tunnel.

of the transverse colon at the site of the tunnel through the root of the mesentery may readily occur. Ten cases of this kind have been collected (table 2).

*Third Stage of Rotation.*—This stage is characterized by the descent and fixation of the cecum in its normal position, the fixation of the descending colon and the fixation of the lower portion of the duodenum.

5. Haymond, H. E., and Dragstedt, L. R.: *Anomalies of Intestinal Rotation*, Surg., Gynec. & Obst. **53**:316, 1931.

6. Lickley, J. D., and Cameron, J.: *Note on a Case of Abnormal Disposition of the Peritoneum*, J. Anat. & Physiol. **41**:88, 1906.

It is completed about the time of birth. The important feature of this stage is the fixation of the cecum in the right iliac fossa so that the mass of small intestine originally dependent from a narrow pedicle at the origin of the superior mesenteric artery acquires a broad oblique attachment to the posterior abdominal wall. It is the absence of this broad attachment which predisposes to volvulus of the entire mesentery.

Failure of the cecum to elongate and undergo early fixation explains the subhepatic and lumbar positions of this organ. Deficient fixation of the ileocecal segment predisposes to the formation of a volvulus of the cecum or ileocecal segment. No attempt has been made to include any of the latter conditions in this presentation.

#### REPORT OF CASES

Two cases of volvulus of the entire mesentery secondary to anomalies in intestinal rotation with symptoms of duodenal obstruction are as follows:

CASE 1.—R. B., a white boy, aged 6 years, was admitted to the Duke Hospital in the pediatric service of Dr. W. C. Davison on July 15, 1932, complaining of intermittent attacks of cramping abdominal pain and vomiting since birth. The patient was the eighth of ten children of healthy parents; he had been born spontaneously at term, weighing  $8\frac{1}{2}$  pounds (3,854 Gm.) at birth. The first feedings were taken normally. On the third day after birth forceful vomiting of bile-stained material began to occur regularly following each feeding. At the age of 5 weeks the child weighed only  $4\frac{1}{2}$  pounds (2,030 Gm.). The mother stated that at that time the fontanels and abdomen were sunken in and the child so feeble that she expected it to die at any moment. For a time thereafter there was improvement. However, from three days after birth until the time of admission the patient had had recurring attacks of abdominal cramps and vomiting of from one to three weeks' duration with intervals between attacks never exceeding five weeks. Development had been normal although he had always been underweight. Attacks were often initiated by overeating, and the accompanying abdominal cramps were usually relieved by vomiting. Bowel movements were scanty but not abnormal during attacks.

The patient was an undernourished boy of 6 years in no discomfort. He weighed 33 pounds (15 Kg.) and was 102 cm. in height. The abdomen was flat and of normal contour. No peristalsis was seen, no tenderness elicited and no masses felt. The superficial veins over the abdominal wall were moderately dilated. Except for evidences of chronic infection in the tonsils the remainder of the physical examination gave normal results.

The hemoglobin was 83 per cent (Sahli); the red blood cells numbered 4,320,000, and the white blood cells, 5,000; the differential count was normal. The tuberculin reaction was positive. The Wassermann test of the blood was negative. The blood calcium was 10.2 mg. per hundred cubic centimeters of blood; the phosphorus, 3.6 mg., and the nonprotein nitrogen, 46 mg. The carbon dioxide-combining power was 67.3 volumes per cent, and the sodium chloride 493 mg. per hundred cubic centimeters on one occasion and 428 mg. on another. Gastric analysis showed: no free hydrochloric acid and 15 combined in the fasting residue; 45 free and 57.9 total acidity after histamine and alcohol.

On July 19 after a barium sulphate meal the first and second portions of the duodenum were found to be enormously dilated (fig. 11) and entirely on the right

of the vertebral column. There was a 25 per cent gastric residue after six hours. This was attributed to an obstruction in the third part of the duodenum. At twenty-four hours the colon was filled and in normal position.

The child remained in the hospital for five and one-half weeks. During this time he suffered seven attacks of cramps in the upper part of the abdomen followed and relieved by vomiting of bile-stained material containing food residue. As operation was not agreed on he returned home on August 26.

Twenty-six days after discharge he was readmitted to the hospital for operation. During the interval he had had almost daily attacks of cramping abdominal pain. There were no changes in the physical findings except for the presence of fulness in the upper part of the abdomen. No peristalsis was visible.

Operation was performed on September 27 by one of us (D. H.). The abdomen was opened through a right rectus incision. The upper part of the abdomen was explored on the right side, and the duodenum was found to be

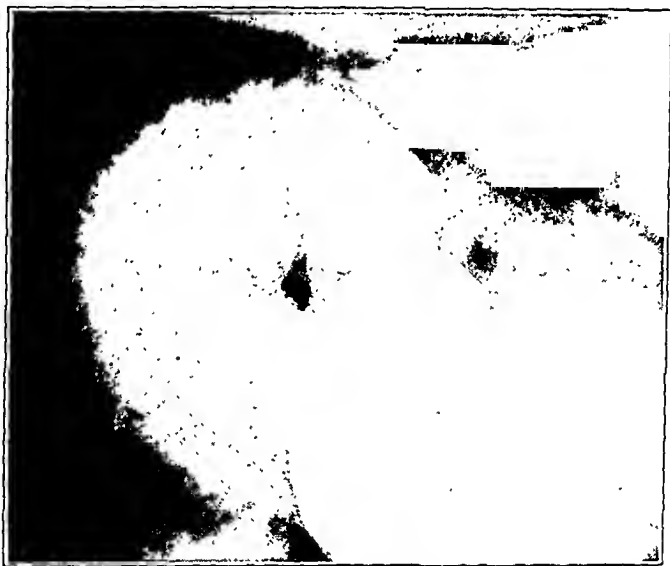


Fig. 11.—Roentgenogram of the barium-filled stomach and duodenum in case 1. The tremendous dilatation of the duodenum is evident. Fluoroscopic examination showed that the duodenum lay entirely on the right of the vertebral column.

dilated. The transverse colon was then lifted up to expose the duodenojejunal junction, but this was concealed by numerous loops of small intestine. It was noted, however, that all the veins to the ascending colon were markedly dilated. The hand was inserted into the abdomen for palpation, and the fingers immediately passed around a tight bandlike structure at the duodenojejunal junction. The exact nature of this structure could not be determined, but on exposing it for inspection it was seen that the cecum was fixed in normal position and that for a distance of about 4 inches (10.16 cm.) the terminal ileum was collapsed and stretched tightly from the ileocecal valve to a point at which it disappeared around the root of the mesentery (fig. 12). The veins to this part of the ileum were extremely dilated. On inspection of the remainder of the small intestine it was seen that the lymphatics were dilated, the lymph nodes greatly enlarged and the veins markedly distended. The tissues were moderately cyanotic. The small intestine was collapsed.

In order to correct the anomaly it was necessary to deliver all of the small intestine. It was then seen that there was a 360 degree clockwise rotation of the root of the mesentery. All of the small intestine was involved except the duodenum and the lower few inches of the ileum (fig. 12). The lumen of the intestine was compressed at the duodenojejunal junction. The mesentery was untwisted, and it was then found that the proximal jejunum and terminal ileum were adherent over a distance of approximately 3 inches (7.62 cm.) (fig. 13). The jejunum and ileum were separated, and the dissection was carried between the mesenteric vessels

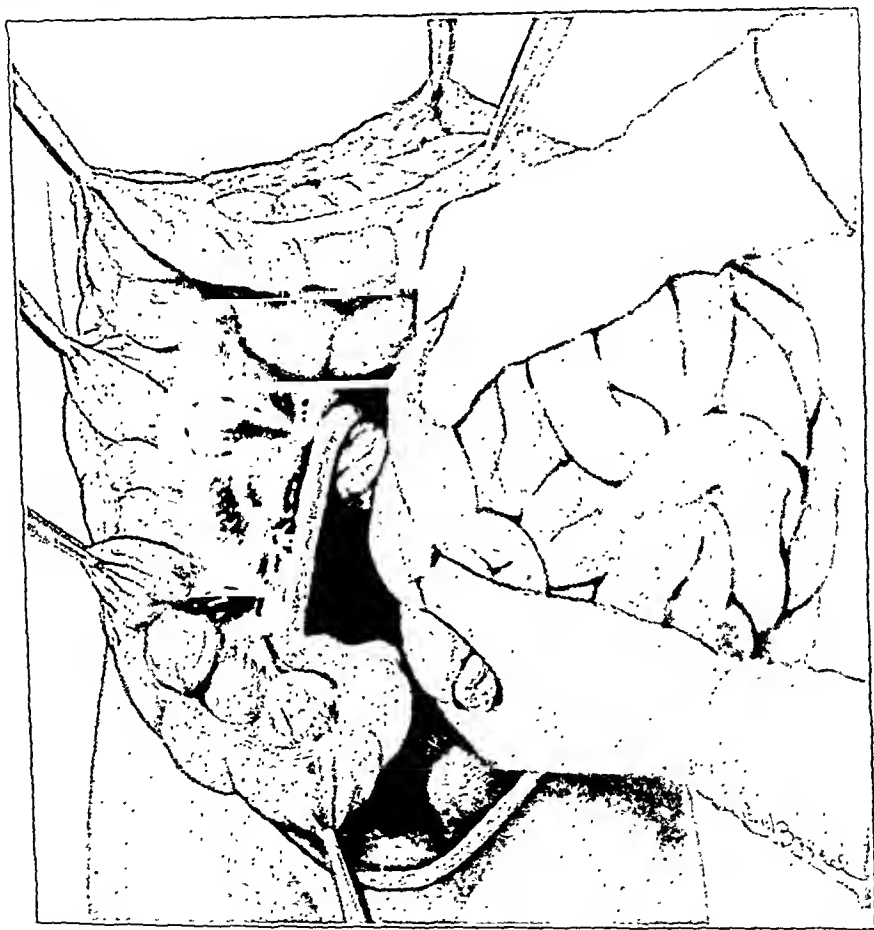


Fig. 12 (case 1).—Appearance on opening the abdomen (from a sketch made during the operation). A 360 degree clockwise rotation of the entire small intestine has taken place. Dilated veins and lymphatic vessels and enlarged lymph glands in the right half of the mesocolon are apparent. The ascending colon has its normal attachment; the duodenum, however, is entirely on the right of the vertebral column.

of the two loops so that the jejunum could be carried into the upper left quadrant and the ileum into the lower right quadrant (fig. 14). The small intestine was then returned to the abdominal cavity so as to lie between the two loops and hold them in the position shown in figure 14. The abdominal incision was closed in layers with catgut for the peritoneum and silk for the fascia, subcutaneous tissue and skin.



Fig. 13 (case 1).—Appearance after detorsion, showing the adhesions between the terminal ileum and the first part of the jejunum. The mesentery of these segments was also firmly adherent from the bowel to the attachment of the root of the mesentery to the posterior abdominal wall.

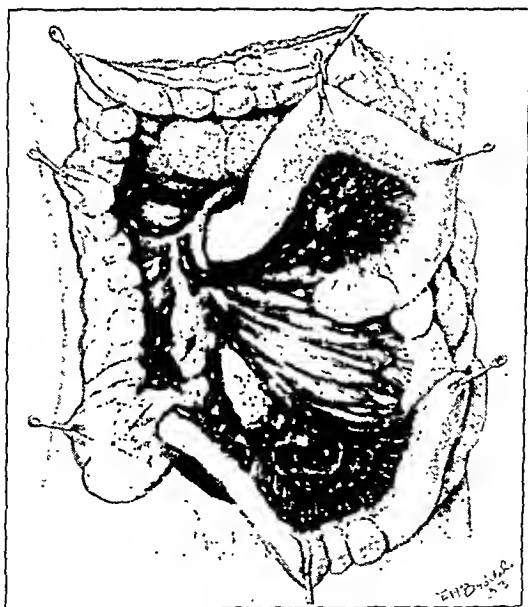


Fig. 14 (case 1).—Appearance at the end of operation. The two segments of bowel, with their mesenteries previously adherent, have been separated. The root of the mesentery is attached to the posterior abdominal wall over a distance of only about 3 cm. Enlarged veins, lymphatic vessels and lymph nodes in the mesentery of the midgut are shown. This enlargement is due to the long-standing partial obstruction of the veins and lymphatics at the point of the twist.

The postoperative convalescence was without event. Roentgen examination fifteen days after operation showed that the stomach and duodenum were still moderately dilated, but there was no gastric retention, and barium passed readily into the jejunum. The patient was discharged sixteen days after operation. A letter from the mother five months later reported that the child had been entirely relieved of all symptoms, that he ate anything he wished and weighed 41½ pounds (19 Kg.). The tonsils had been removed in February. The only unusual feature noticed by his mother was the occurrence of from three to five bowel movements a day.

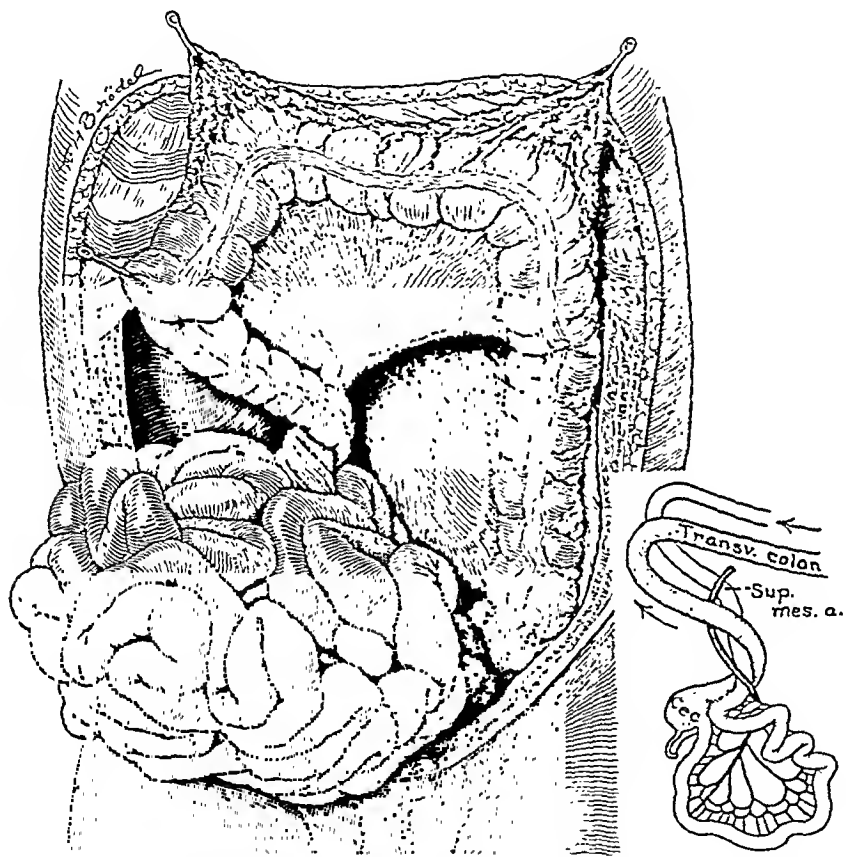


Fig. 15 (case 2).—Appearance on opening the abdomen (from a sketch made during operation). The hepatic flexure of the colon has become fixed normally; the cecum and ascending colon, however, remain suspended with the small intestine on a common mesentery. A 360 degree clockwise rotation of the entire small intestine, cecum and part of the ascending colon has taken place.

CASE 2.—M. M., a colored boy, aged 2 months, was admitted to Duke Hospital in the pediatric service of Dr. W. C. Davison on Oct. 21, 1932, with a complaint of persistent vomiting for one month and pain and disability of the right arm for one week. The child, the first of apparently healthy parents, was born spontaneously at term, and weighed 7 pounds (3,175 Gm.) at birth. He had been normal in all respects until the age of 1 month when he began vomiting bile-stained material after one or two feedings each day. This had persisted until admission. The stools had remained normal, and there had been no loss of weight. In the



five days prior to entry pain and swelling of the right arm just above the elbow had developed, and the child had refused to use the arm.

The patient was a well developed, fairly well nourished male Negro infant of 2 months. He weighed 11 pounds (5.2 Kg.). There was no evidence of dehydration. The lower third of the upper part of the right arm was moderately and diffusely swollen, tender and indurated. The child did not use the right arm and resented motion at the elbow. The abdomen was full in the epigastric region. No peristalsis was seen, no tenderness elicited and no masses felt.

The hemoglobin was 45 per cent (Sahli); the red cell count was 3,110,000, and the white cell count, 10,400; the differential count was normal. The Schick, Dick

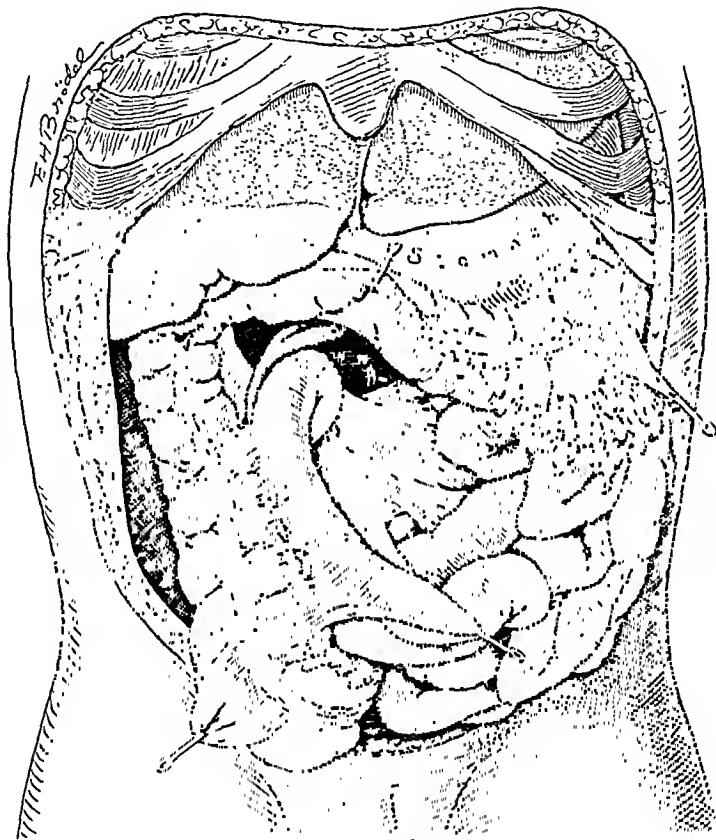


Fig. 16 (case 2).—Appearance after detorsion. The duodenum is dilated and entirely on the right of the midline. As in case 1 there are adhesions between the proximal and distal parts of intestine involved in the volvulus.

and tuberculin tests were negative. The Wassermann reaction of the blood was 4+. A roentgenogram of the right humerus showed a rarefaction and periostitis throughout the lower third with a fracture through the diaphysis.

Following a barium meal, obstruction in the third portion of the duodenum with dilatation of the duodenum and stomach was noted, and there was a small gastric retention after twenty hours. The colon was not filled at twenty hours. A barium enema showed an obstruction in the transverse colon.

During a ten day stay in the hospital the child vomited between 30 and 350 cc. of bile-stained material daily. The weight remained stationary. The lesion in the bone was considered as due to congenital syphilis, and the abdominal condition was diagnosed as volvulus of the entire midgut.

Operation was performed by one of us (D. H.) on Nov. 2, 1932. The abdomen was opened through a right rectus incision. A dilated stomach and duodenum immediately presented. The hepatic flexure of the colon was fixed in its normal position, and the ascending colon was seen to run from this point of fixation medially and downward until it disappeared in a twist around the root of the mesentery (fig. 15). It was immediately concluded that there was a volvulus of the intestinal tract from the duodenojejunal junction almost to the hepatic flexure of the colon. The rotated intestine was delivered. The twist was seen to be about

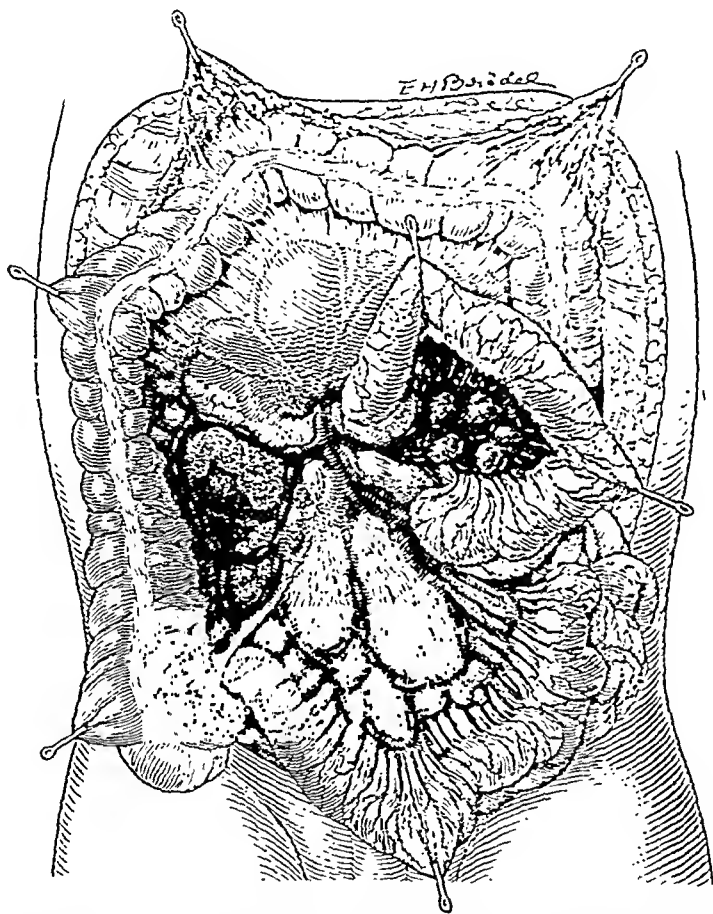


Fig. 17 (case 2).—Appearance after liberation of the adhesions. In the mesentery of the midgut there are dilated veins and lymphatics and enlarged lymph nodes as in case 1.

360 degrees in a clockwise direction. The veins and lymphatic vessels were dilated, though not as markedly as in case 1. The lymph glands were moderately enlarged. When the bowel was untwisted it was found that the cecum and lower part of the ascending colon were freely movable. The upper part of the ascending colon was adherent to the proximal part of the jejunum (fig. 16).

The two structures were dissected free, and the dissection was carried down between the mesenteries of each so that the cecum could be placed in the right lower quadrant and the proximal jejunum in the left upper quadrant (fig. 17). The small intestines were returned to the abdominal cavity so as to lie between

TABLE 1.—*Volvulus of the Entire Mesentery*

Case	Author	Year	Sex	Age	Symptoms and Signs	Bowel in Volvulus	Direction and Degree	Result
1	Kuljazbo and Koreski	1847	M	22	Attacks of abdominal colic, vomiting and diarrhœa since childhood; present attack for 5 days; condition not recognized at operation; death on day of operation	Small intestine and ascending colon	4 turns	Death after operation
2	Bednar: Die Krankheiten der Neugeborenen und Sudhinge, Vienna, C. Gerold, 1850, vol. 1, p. 127	1850	M	New-born	Normal bowel movements but persistent vomiting for 2 days before death; abdomen soft and not distended; death on ninth day	Small intestine and ascending colon	180 degrees clockwise	Death without operation
3	Leonard: Arch. gén. de méd. 1854, p. 242; quoted by Ekehorn, Arch. f. Klin. Chir. 72: 572, 1904	1854	M	20	Death after 9 days, suffering from ileus; no operation; at autopsy small intestine distended and filled with blood	Small intestine and ascending colon	350 degrees clockwise	Death without operation
4	Eppinger: Prag. Vrtjschr. f. pract. Heilk. 117: 61, 1873	1873	F	New-born	No clinical history; death with autopsy on fourth day; small intestine, cœcum and ascending colon on common mesentery	Small intestine	180 degrees clockwise	Death without operation
5	Whipham, T. T.: M. Times & Gaz. 2: 33, 1876	1876	F	10	Similar attack 18 months previously; since then recurring attacks of abdominal cramps; seen on tenth day of illness with intestinal colic, vomiting of greenish material and obstipation; abdomen not distended; death on twelfth day; duodenum obstructed; bowel collapsed	Small intestine and ascending colon	Contra-clockwise	Death without operation
6	Firth, C.: Brit. M. J. 2: 1882	1882	M	40	Abrupt onset 5 days before entry with abdominal pain, vomiting and enlargement of hernia present for 5 years; fecal vomiting on admission; hernia easily reduced; condition not recognized at operation; death 3 days later; autopsy	Small intestine and ascending colon	340 degrees	Death after operation
7	Brulius: St. Petersb. med. Wehnschr. 7: 321, 1883	1883	M	24	Seen on fifth day of illness with symptoms of ileus; had had three previous similar attacks, the first 10 years previously; abdomen distended; peristaltic patterns visible; death 40 minutes after operation	Entire midgut	360 degrees clockwise	Death 40 minutes after operation with detorsion
8	Theremin, E.: Deutsche Ztschr. f. Chir. 8: 34, 1877	1877	F	New-born	Vomiting of greenish material beginning on day after birth; abdomen somewhat distended; veins of epigastric region engorged; ineffectual enemas; death on third day	Small intestine and ascending colon	3½ turns clockwise	Death without operation
9	Theremin	1877	M	New-born	Vomiting of bile-stained material since birth; death on sixteenth day; autopsy	Small intestine and ascending colon	2 turns contra-clockwise	Death without operation
10	Sovka-Epstein: Prag. med. Wehnschr. 12: 463, 1878	1878	..	New-born	Illness on fourth day with forceful and repeated vomiting and death on tenth day; at autopsy stomach and first part of duodenum tremendously distended	Small intestine and ascending colon	180 degrees clockwise	Death without operation
11	Brown, W. R.: Tr. Indian Branch Brit. M. A. 5: 5, 1895; quoted by Vaughn, G. T.: Am. J. M. Sc. 75: 799, 1903	1895	M	50	Operation 5 days after onset of colicky abdominal pain and constipation; abdomen distended; at operation, cœcum on left side and small intestine distended	Small intestine	Contra-clockwise	Well after detorsion
12	Boyd, F. N.: Lancet 2: 8, 1897	1897	F	39	For 6 years pain on eating relieved by vomiting; occasionally blood in stools and vomitus; ill 10 days with symptoms of ileus; abdomen distended; operation on tenth day, condition not recognized; autopsy	Small intestine and ascending colon	360 degrees contra-clockwise	Death after operation

13	Key, 1897, quoted by Bren- ner 43	1897	M	Adult	Symptoms of ileus; operation on fourteenth day; con- dition not recognized; colostomy done; autopsy eleventh day	Small intestine and ascending colon	360 degrees	Death after operation
14	Wettersleb; Zentralbl. Chir. 51: 286, 1898	1898	M	42	Sudden illness with symptoms of ileus; operation on eleventh day	Small intestine and ascending colon	220 degrees clockwise	Wall after detorsion
15	Helmstaedt 22	1898	M	20	Sudden onset after violent jump; severe abdominal pain; collapse; death after 6 hours; at autopsy bloody pri- mordial fluid and intestine filled with blood	Entire midgut	260 degrees contra- clockwise	Death without operation
16	Schroeder, E.; Ztschr. f. klin. Med. 35: 426, 1899	1899	M	9	Repeated attacks of abdominal pain, vomiting and consti- pation since birth; death on fifth day of attack; vomitus voluntarily greenish intestinal, never fecal; abdomen moderately distended; at autopsy stomach and duodenum tremendously distended	Small intestine and ascending colon	360 degrees contra- clockwise	Death without operation
17	von Muntenfels, L.; Samml. klin. Vortr. no. 260, 1899, p. 1421	1899	M	20	After lifting sack of grain, cramping abdominal pain with vomiting of bile-stained material and constipation; no abdominal distention; operation on sixth day; death 3 days later	Small intestine and ascending colon	90 degrees clockwise	Death after operation
18	Hausmann 20	1900	M	22	Four similar previous attacks; operation on fifth day of intestinal obstruction; reversed rotation with removal ileocecal mesentery; kink at hepatic flexure straightened allowing feces to pass; death on following day; at autopsy, postoperative volvulus of entire small intestine with cecum in region of spleen; position of cecum nor- mal at first operation	Small intestine	180 degrees contra- clockwise	Death after operation
19	Durrante 23	1901	..	New- born	Persistent vomiting since birth; vomitus contained some blood; blood passed per rectum; death on third day	Entire midgut	450 degrees clockwise	Death without operation
20	Pröllsch; Bull. et mém. Soc. de chir. de Paris 27: 512, 1901	1901	M	3	Abdominal pain, vomiting, constipation and distention for 15 days; condition not recognized at operation; death in 36 hours; autopsy	Entire midgut	Contra- clockwise	Death after operation
21	Blecher 20	1902	M	25	Sudden onset of abdominal pain with collapse and vomit- ing of bile-stained material; no distention; death during operation 12 hours after onset; bloody peritoneal fluid, blood in intestine	Small intestine and ascending colon	220 degrees contra- clockwise	Death during operation
22	Burgess, A. H.; Lancet 2: 1690, 1902	1902	M	8	Sudden onset, acute abdominal pain with vomiting of greenish material, no distention; collapse; death 16 hours after onset	Small intestine and ascending colon	220 degrees clockwise	Death without operation
23	Kroghs-Fantini; Nord. med. ark. 2: 80, 1903	1903	F	21	Recurring attacks of abdominal pain for several years; operation after 4 days of abdominal colic, vomiting and constipation; death on fifth day	Small intestine and ascending colon	1½ turns clockwise	Death after operation
24	Wandel; Mitt. n. d. Grenz- geb. d. Med. u. Chir. 11: 51, 1903	1903	M	7	Periodic attacks of abdominal pain, vomiting and consti- pation since birth; sudden attack 6 days after fracture of left femur; vomitus bile-stained; abdomen not dis- tended; death on fourteenth day; duodenum obstructed	Small intestine and ascending colon	240 degrees clockwise	Death without operation
25	Pesentore, M.; Deutsche Ztschr. f. chir. 48: 185, 1903	1903	M	New- born	No clinical history given; autopsy on nineteenth day; duodenum enormously dilated	Small intestine and ascending colon	1½ turns clockwise	Death without operation
26	Ekholm, G.; Arch. f. klin. Chir. 72: 572, 1904	1904	F	15	Illness for 3 weeks with abdominal pain and vomiting; abdomen distended, vomitus fecal; death 10 hours after detorsion and resection of ganglions cecum and ascending colon	Small intestine and ascending colon	230 degrees clockwise	Death after operation

TABLE 1.—*Volvulus of the Entire Mesentery—Continued*

Case	Author	Year	Sex	Age	Symptoms and Signs	Bowel in Volvulus	Direction and Degree	Result
27	Möhring: Deutsche med. Wochenschr. 1: 162, 1905	1905	F	72	Recurring attacks of abdominal pain with constipation for 1 year; recently frequent vomiting; abdomen distended; fecal material in stomach; operation; bloody peritoneal fluid	Small intestine and ascending colon	180 degrees clockwise	Well after detorsion
28	Danielson, W. and Kuttner: Beitr. z. klin. Chir. 48: 100, 1906	1906	F	55	Abdominal pain, vomiting and constipation for 4 days; abdomen distended; peristalsis present; death from peritonitis 9 days after operation	Small intestine and ascending colon	360 degrees clockwise	Death after detorsion
29	Clément, P.: Ann. de gynéc. et d'obst. 3: 567, 1906	1906	..	New-born	Child normal at birth; took feedings well and passed meconium; on second day abdomen and veins of abdominal wall became distended; death on second day of illness	Entire midgut	2 turns clockwise	Death without operation
30	Müller, E.: Zentralbl. f. allg. Path. u. path. Anat. 20: 514, 1909	1909	M	New-born	Death with autopsy on fifth day; no clinical history given	Small intestine and ascending colon	360 degrees clockwise	Death without operation
31	Müller .....	1909	F	15	Frequent attacks of abdominal cramps with vomiting since age of 2; death in collapse during an attack; autopsy, common ileocecal mesentery	Small intestine	2 turns clockwise	Death without operation
32	Billington, W.: Lancet 1: 1909	1909	M	41	Attacks of abdominal cramps with vomiting lasting 2 or 3 days every 8 or 9 months for 4 years; seen on sixth day of attack; abdomen moderately distended; swelling in left upper quadrant later found to be caused by enormously distended cecum; operation on sixth day	Small intestine and ascending colon	Not given	Well after detorsion
33	Blecher: Deutsche Zeitschr. f. Chir. 98: 521, 1909	1909	M	20	Several previous attacks of abdominal pain and vomiting; operation on second day of an attack; vomiting of bile-stained material containing a worm; two stools of bright blood; abdomen not distended; preoperative diagnosis, mesenteric thrombosis or intussusception	Small intestine and ascending colon	180 degrees contralockwise	Well after detorsion
34	Hubner .....	1910	M	3	Attacks of abdominal colic with vomiting at 4 to 8 week intervals; seen in an attack; abdomen moderately distended; cysts palpable in epigastrium and lower left quadrant; at operation mesenteric cyst and 6 cm. of small bowel resected; death on following day; autopsy showed volvulus of midgut	Entire midgut	360 degrees	Death after operation
35	Michelis .....	1913	M	New-born	Normal delivery; passed meconium; on second day went into collapse, passed blood in stool; death on following day	Small intestine and ascending colon	1½ turns contralockwise	Death without operation
36	Webble, R. E.: Surg. Gynec. & Obst. 19: 644, 1914	1914	M	27	Attacks of colic and abdominal distention all his life; seen on third day of an attack; had had diarrhea for first 2 days; enemas ineffectual on third day; vomited dark material; moderate distention; common ileocecal mesentery	Small intestine	180 degrees clockwise	Well after detorsion
37	Fischbach, quoted by Welble: Surg. Gynec. & Obst. 19: 644, 1914	1914	M	New-born	Death with autopsy on eighth day; no clinical history given	Entire midgut	Clockwise	Death without operation

					Small intestine and ascending colon	300 degrees contra- clockwise	Death after detorsion
38	Köhler <sup>32</sup>	1918	F	23	Entire midgut	1½ turns clockwise	Well after detorsion and colopexy
39	Outrebonne, L.; Bull. et Mém. Soc. de chir. Paris 455 1888, 1919	1919	F	11	Entire midgut	350 degrees clockwise	Well after detorsion
40	Risford <sup>31</sup>	1920	M	5	Entire midgut	3 turns clockwise	Death after operation
41	Kolzareff, A.; Bull. et Mém. Soc. de chir. 461; 577, 1920	1920	M	12	Entire midgut	180 degrees contra- clockwise	Death without operation
42	Hammann <sup>31</sup>	1922	M	23	Entire midgut	180 degrees clockwise	Well after detorsion
43	Eggers, O.; Ann. Surg. 75; 757, 1922	1922	F	30	Small intestine and ascending colon	180 degrees clockwise	Well after detorsion and colopexy
44	Heymann <sup>41</sup>	1922	M	31	Small intestine and ascending colon	180 degrees clockwise	Well after detorsion and colopexy
45	Heymann <sup>41</sup>	1922	M	20	Small intestine and ascending colon	180 degrees clockwise	Death after gastrojejunostomy
46	Dott <sup>4</sup>	1923	M	New-born	Entire midgut	180 degrees clockwise	Death after gastroenterostomy
47	Dott <sup>4</sup>	1923	F	New-born	Small intestine	180 degrees clockwise	Death after gastroenterostomy

Sudden onset of severe abdominal pain while at work; no vomiting; seen after 3 hours in collapse; pulse full and rapid; abdomen distended; immediate operation; diagnosis of ruptured ectopic pregnancy; blood-stained abdominal fluid; intestines filled with blood; vomited blood after operation

Since age of 18 months repeated frequent attacks of vomiting; daily vomiting of large amounts of bile-stained material for 3 months before operation; dehydration, emaciation; gastric tetany; no distention; roentgen rays showed duodenal obstruction

Recurring attacks of colic and vomiting since birth; never had been able to take a full meal without inducing an attack; emaciation; unable to be up more than a few hours a day because of weakness; abdomen distended in epigastrium, scapula below

No clinical history given; autopsy showed obstruction to third part of duodenum; also abnormality of mesenteric arteries

Recurring attacks of colic and vomiting since birth; operation for acute appendicitis; cecum mobile but on right side; on fifth day, intestinal obstruction; death on ninth day; autopsy, cecum on left side; duodenum obstructed at autopsy, cecum on left side; duodenum without vomiting

Intermittent attacks of abdominal pain without vomiting for 10 years; seen on second day of attack; abdomen distended; operation; patient also had large hydrous of appendix

Recurring attacks of abdominal pain and vomiting for 6 years, aggravated by taking food; emaciation; gastric retention on roentgen examination; at operation, cecum adherent in pelvic fossa with 180 degree clockwise volvulus of small intestine and ascending colon; also duodenal ulcer; Juddroth 1 resection of stomach, detorsion and colopexy

Multise and indolent abdominal pain for 6 months; sudden attack, severe epigastric pain 3 weeks before; nausea, anorexia and constipation since then; roentgen examination showed duodenal obstruction; operation; cecum adherent to duodenum with resolving abscess of appendix behind duodenum

Normal for 5 days; then vomiting after feedings; vomitus green colored; stools normal for 5 days, then a little blood noticed in one stool; vomiting regularly 25 minutes after feeding; no distention; gastric peristalsis visible on seventh day of illness; operation; obstruction at duodenum; death after 12 hours

Normal for 3 days, then began vomiting after feeding; vomitus soon bile stained and on third day contained a little blood; based incision per rectum but never noticed stool; upper part of abdomen distended and gastric peristalsis visible; emaciated and dehydrated; operation; obstruction at duodenum; death after 7 hours; autopsy showed malrotation and deficient fixation of midgut

TABLE 1.—*Volvulus of the Entire Mesentery*—Continued

Case	Author	Year	Sex	Age	Symptoms and Signs	Bowel in Volvulus	Direction and Degree	Result
48	Brachung <sup>12</sup>	1924	M	21	Previously healthy; operation after 3 hours of symptoms of acute strangulation; ileus; found reversed rotation with volvulus of entire small intestine, cecum and ascending colon; obstruction at hepatic flexure	Small intestine and ascending colon	300 degrees clockwise	Death after resection of cecum and ascending colon
49	Poynton, F. J.: Lancet 1: 1034, 1924	1924	F	3	Recurring attacks of vomiting and abdominal pain aggravated by meals since age of 1 month; attacks at intervals of from 6 to 8 weeks lasting 3 or 4 days; seen on fifth day of an attack, vomiting feculent material; abdominal pain and obstipation; passed an offensive stool on sixth day; no abdominal distention; death on eighth day; autopsy showed common ileocecal mesentery	Small intestine	300 degrees clockwise	Death without operation
50	Poynton	1924	M	3½	Attacks of abdominal pain and vomiting at age of 5 and 7 months; seen on fourth day of attack; abdominal pain, vomiting of thick greenish material and obstipation; no abdominal distention; death on eighth day; at autopsy common ileocecal mesentery with cecum in region of spleen	Small intestine	1½ turns clockwise	Death without operation
51	Poynton	1924	M	12	Recurring attacks of abdominal pain and vomiting for 2½ years; autopsy after death in an attack	Small intestine	2 turns contra-clockwise	Death without operation
52	Wheeler, J. B.: Boston M. & S. J. 190: 230, 1924	1924	F	8	Repeated attacks of vomiting and abdominal pain since birth; admitted on second day of attack with vomiting of greenish material, abdominal pain and obstipation; no abdominal distention; at operation bowel collapsed; long mesentery	Small intestine	1½ turns clockwise	Well after detorsion
53	Baker, A. H., and Mizen, V.: Brit. M. J. 1: 1031, 1926	1926	M	New-born	Normal for 6 days; then vomiting 20 to 30 minutes after feedings; vomitus bile-stained on second day; stools normal at first, then contained only greenish mucus; visible gastric peristalsis on fifth day; lower abdomen scaphoid; death on tenth day	Entire midgut	180 degrees clockwise	Death without operation
54	Schöttle, A.: Deutsche Zeitschr. f. Chir. 194: 401, 1926	1926	F	23	Attacks of abdominal pain and constipation for 3 years; for preceding 6 weeks vomiting and abdominal colic after meals; roentgen examination showed duodenal obstruction with 20 per cent gastric retention in 4 hours; operation	Entire midgut	360 degrees clockwise	Well after detorsion
55	Schöttle	1926	F	30	Pain in lower part of abdomen; belching and constipation for 2 weeks, more severe for 2 days; abdomen moderately distended, tender in its lower half; operation for appendicitis; ascaris passed in stools after operation	Small intestine and ascending colon	180 degrees clockwise	Well after detorsion and cecopexy
56	Valkanyl, R.: Paris méd. 1: 95 (Jan. 23) 1926	1926	..	New-born	Premature birth (eighth month); normal for 1 week; on eighth day, after a bath, vomiting, obstipation and distention; operation, death next day; autopsy showed common ileocecal mesentery	Small intestine	Not given	Death after detorsion
57	Lawson <sup>27</sup>	1927	M	40	For 4 years frequent attacks of abdominal pain and vomiting; admitted moribund on fifth day of an attack; had passed pinkish fluid by rectum on the fourth day; at necropsy, dorsal attachment of mesentery 1 inch (2.54 cm.) in length	Small intestine	720 degrees contra-clockwise	Death without operation

No.	Author	Year	Sex	Age	History	Post-mortem	Remarks
58	Strecker, F. M.; Hirt, M. J.	1927	M	New-born	Normal delivery; passed meconium; on second day refused to nurse, seemed in pain; abdomen slightly distended; no stool; operation on second day; death 4 hours later.	Small intestine	300 degrees clockwise
59	Pinkerton	1927	M	New-born	Normal delivery; on second day, vomiting of dark green mucus; thereafter vomiting from 25 to 30 minutes after feedings; seen at age of 4 weeks; passing blood by rectum in quantities; roentgen examination showed duodenal occlusion; operation on twenty-fifth day.	Small intestine and ascending colon	2 1/2 turns clockwise
60	Donald	1927	F	27	Epileptic, 5 months pregnant; an attack of intestinal colic 3 years previously; typical signs and symptoms of intestinal obstruction of 2 1/2 hours' duration; operation; reversed rotation with volvulus of small intestine and ascending colon.	Small intestine	300 degrees clockwise
61	Dott	1927	F	New-born	Normal birth; passed meconium; on fourth day suddenly seemed in abdominal pain; vomitus at first clear, then bile-stained; obstipation; blood-stained mucus passed per rectum on eighth day; dehydration; distention of upper part of abdomen; at operation common ileocecal mesentery; duodenum obstructed by root of mesentery; small bowel collapsed.	Small intestine and ascending colon	300 degrees clockwise
62	Oberling	1927	M	New-born	Seen (unborn) on fifth day; history of having vomited everything taken by mouth since birth; vomitus blood-stained; autopsy, bloody peritoneal fluid, duodenum compressed by root of mesentery.	Small intestine and ascending colon	3 turns clockwise
63	Oberling	1927	M	New-born	Death on ninth day; no clinical history.	Entire midgut	300 degrees clockwise
64	Oberling	1927	M	12	Frequent attacks of vomiting since birth; death in collapse during an attack; at autopsy duodenum tremendously dilated.	Small intestine	300 degrees clockwise
65	Larsen, G.; Arch. Ital. di chir.	1928	M	11	Periodic attacks of abdominal pain every 20 to 30 days since birth; attacks aggravated by solid foods; roentgen examination showed left-sided colon; at operation cecum and ascending colon fixed in left hypochondrium; common ileocecal mesentery.	Small intestine	300 degrees clockwise
66	Radnell	1928	F	15	Painful in ninth month of pregnancy previously without symptoms; complicated suddenly of violent abdominal pain; vomiting, collapse; death 22 hours after cesarean section; volvulus not recognized at operation; autopsy.	Small intestine and ascending colon	150 degrees clockwise
67	Last, M. and Bourg, R.; Bruxelles-méd.	1928	M	New-born	Normal until second day; passed meconium; projectile vomiting of bile-stained material beginning on second day until death on seventh day; superficial abdominal veins dilated.	Entire midgut	150 degrees clockwise
68	Chursley and Richardson	1928	M	New-born	Vomiting green fluid since birth; dark bowel movements which on third day became fluid blood; blood passed constantly from rectum in quantity; abdomen soft; cecostomy distended; death on sixth day; at autopsy blood-stained peritoneal fluid; root of mesentery very short; bowel gangrenous.	Small intestine	150 degrees clockwise
69	Schram-Andersen, J.; Rev. franc. de pédiat.	1929	F	1 month	Repeated attacks of vomiting of bile-stained material; abdominal distention since birth; roentgen examination showed gastric retention and left-sided colon; death 15 hours after operation.	Small intestine and ascending colon	150 degrees clockwise



TABLE 1.—*Volvulus of the Entire Mesentery*—Continued

Case	Author	Year	Sex	Age	Symptoms and Signs	Bowel In Volvulus	Direction and Degree	Result
70	Mole, R. H.: Brit. J. Surg. 17: 670, 1930	1930	F	8	Attacks of epigastric pain, vomiting and malaise of 3 to 7 days' duration every 4 to 6 months since birth; final attack of 7 days' duration with copious vomiting of bile-stained material and obstipation; at autopsy, duodenum obstructed	Entire midgut	180 degrees clockwise	Death without operation
71	Skinner, A. H.: China M. J. 44: 53, 1930	1930	M	New-born	History of vomiting since birth; had passed meconium; upper abdomen distended; operation on second day; condition not recognized; at autopsy, root of mesentery only three fingerbreadths in length	Small intestine	180 degrees clockwise	Death after operation
72	Moulounguet, Doleris and d'Aubigne: Bull. et mèm. Soc. de chir. de Paris 56: 122, 1930	1930	M	21	Since age of 11, intermittent attacks of vomiting; patient emaciated, dehydrated; recent persistent vomiting of bile; at first operation detorsion of volvulus; returned at request after 4 months for cecopy	Small intestine and ascending colon	150 degrees clockwise	Well after detorsion
73	Moulounguet, Doleris and d'Aubigne	1930	M	53	Colicky abdominal pain of 24 hours' duration; no vomiting; moderate distention; operation	Small intestine and ascending colon	360 degrees clockwise	Death after detorsion and cecopy
74	Haymond and Drugstedt	1931	M	16	Since birth intermittent attacks of vomiting at intervals of from 1 to 4 weeks; vomitus bile-stained; attacks aggravated by heavy meals; roentgen examination showed a duodenal obstruction with 33 per cent gastric retention in 5 hours; at operation, cecum in left hypochondrium and common iliocecal mesentery	Small intestine	120 degrees clockwise	Well after detorsion
75	Green, T. M.: Surg., Gynec. & Obst. 53: 734, 1931	1931	F	New-born	Projectile vomiting of all feedings and large quantities of bile since birth; roentgen examination showed duodenal obstruction; operation on tenth day	Entire midgut	1½ turns clockwise	Well after detorsion and fixation
76	Green	1931	F	New-born	Projectile vomiting of all feedings and large quantities of bile since birth; visible gastric peristalsis; operation on fourth day with diagnosis of volvulus of the midgut; adhesions between duodenum and cecum	Small intestine	1¾ turns clockwise	Well after detorsion and fixation
77	Brenner <sup>43</sup>	1932	F	30	Constipation all of her life; attack of abdominal colic 1 year previously; seen after 30 hours of colicky abdominal pain and vomiting; abdomen tremendously distended; visible intestinal peristalsis; operation with detorsion of volvulus of entire midgut; recovery; recurrence of symptoms of acute intestinal obstruction 9 months later; operation after 10 hours; exactly similar condition found as at first operation; well after detorsion and fixation	Entire midgut	360 degrees clockwise	Well after second operation with detorsion and fixation
78	Brenner <sup>43</sup>	1932	F	26	Sudden onset; colicky abdominal pain with vomiting; obstipation and abdominal distention 36 hours previously; abdomen tremendously dilated; operation; proximal half of colon tremendously dilated	Entire midgut	180 degrees clockwise	Well after detorsion and fixation
79	Lee <sup>42</sup>	1932	M	11	Recurring attacks of colicky abdominal pain and vomiting from 4 to 7 days every month since early infancy; roentgen examination showed obstruction in duodenum and left-sided colon; at operation veins in ascending mesocolon tremendously dilated	Small intestine	180 degrees clockwise	Well after duodenojejunostomy and ileocolostomy

No.	Author	Year	Sex	Age	History	Location	Findings	Operation	Result
80	Benham 10	1932	M	20	Infants of sauntering; cerebral diplegia since age of 15; sudden onset of abdominal pain and vomiting; collapse after 10 hours; operation; entire intestinal tract gangrenous	Small intestine and ascending colon	180 degrees clockwise	Death after operation	
81	Moritz 63	1932	M	New-born	Vomiting and constipation since birth; roentgen examination showed duodenal obstruction; operation in third week	Small intestine and ascending colon	360 degrees clockwise	Death after operation	
82	Moritz 15	1932	M	New-born	Vomiting since birth; roentgen examination showed duodenal obstruction; operation at seventh week; volvulus so adherent detorsion not thought possible	Small intestine and ascending colon	360 degrees clockwise	Death after operation	
83	Ladd 30	1932	M	New-born	Projectile vomiting of bile-stained material beginning on eleventh day; visible gastric peristalsis; roentgen examination showed duodenal obstruction; operation on fourteenth day; common ileocecal mesentery	Small intestine	Not given	Well after detorsion	
84	Ladd 30	1932	M	9 mos.	Intermittent vomiting since birth; operation at ninth month with detorsion of volvulus of entire small intestine; common ileocecal mesentery; recurrence of symptoms after 1 month; second operation, detorsion, mobilization of cecum from adhesions in lower left quadrant; recovery	Small intestine	Not given	Well after second detorsion	
85	Ladd 30	1932	F	New-born	Vomiting of bile-stained material since birth; visible gastric peristalsis; operation at 1½ weeks; duodenum obstructed	Entire midgut	120 degrees clockwise	Well after detorsion	
86	Holmes, J. S.; J. Florida M. A., 18:265, 1931	1931	M	35	Periodic attacks of nausea and vomiting between ages of 6 and 11; similar symptoms in past 2 years; roentgen examination showed tremendous dilatation of duodenum; at operation, common ileocecal mesentery	Small intestine	120 degrees	Well after and detorsion and duodenoduodenostomy	
87	Gardner and Hart	1933	M	6	Repeated periodic attacks of abdominal cramps and vomiting of bile since third day after birth; dehydration; malnutrition; abdomen flat; roentgen examination showed duodenum dilated and on right side of vertebral column	Small intestine	270 degrees clockwise	Well after detorsion	
88	Gardner and Hart	1933	M	2 mos.	Vomiting of bile for 1 month; congenital syphilis with involvement of lower part of right humerus; roentgen examination showed duodenal obstruction with gastric retention for 20 hours	Small intestine and ascending colon	270 degrees clockwise	Well after detorsion	

TABLE 2.—*Reversed Rotation with Obstruction of the Colon by Torsion or Kinking*

Case	Author	Year	Sex	Age	Symptoms and Signs	Result
1	Tscherning, E.: Nord. med. ark. 15:1, 1883	1883	M	56	Death with autopsy on nineteenth day of illness with symptoms of intestinal obstruction	Death without operation
2	Clairmont, P.: Arch. f. klin. Chir. 76: 316, 1905	1905	M	48	Abdominal pain with vomiting for 3 years; diagnosis of duodenal ulcer with obstruction to pylorus; at operation, duodenal ulcer found and anterior gastro-enterostomy performed; death 8 days later with signs of ileus; autopsy	Death without operation
3	Strehl, H.: Arch. f. klin. Chir. 87:8, 1908	1908	F	12	Previously healthy; seen on eighth day of illness with lower abdominal cramps and vomiting; abdomen distended; operation; death after 8 hours	Death after cecostomy
4	Hunter 10	1922	..	New-born	Breech delivery at term; did not take feedings well; seemed in constant abdominal pain; bowels kept open with frequent enemias; death on seventh day; at autopsy, reversed rotation and mesenteric cyst of jejunal origin	Death without operation
5	Dott 4	1923	M	68	Acute intestinal obstruction of 3 days' duration; similar attack 10 years previously; abdomen distended; outline of distended ascending colon visible, extending from upper right to lower left quadrant; at operation, reversed rotation with 180 degrees clockwise torsion of ascending colon; gangrenous patches in ascending colon; death 3 days after operation	Death after resection of right half of colon
6	Harvey 35	1926	F	New-born	Vomiting of greenish material and no bowel movements since birth; abdomen distended, especially on right side; operation on third day; gangrenous patches with perforation of ascending colon	Death after operation
7	Walker, H. B.: Edinburgh M. J. 33: 725, 1926	1926	M	28	Acute intestinal obstruction of 24 hours' duration; at operation, adhesion across upper part of abdomen released; actual condition only recognized at autopsy 3 days later; dextrocardia diagnosed clinically; autopsy limited to abdomen	Death after operation; condition not recognized
8	Serek-Hanssen 45	1926	F	21	Attacks of indigestion with vomiting for 1 year; seen in an attack; abdomen distended; enemias ineffectual; at operation, reversed rotation with volvulus of the mobile cecum	Well after detorsion and fixation of cecum
9	Lee 42	1929	M	24	Repeated attacks of abdominal colic as a boy; last attack 4 years previously; seen on fourth day of an attack; vomiting since first day; abdomen distended, especially in right lower quadrant; at operation last two loops of ileum with cecum and ascending colon in reversed position; death 24 hours after evacuating cecum and replacing it through the orifice	Death after operation
10	Pelgneaux and Fruchard 31	1930	F	15	Premature child; repeated attacks of vomiting and abdominal colic since birth; operation during an attack; found reversed rotation with partial obstruction at duodenum and transverse colon	Recovery after anterior gastro-enterostomy and lateral transverse colocolostomy

TABLE 3.—*Duodenal Obstruction from Abnormal Intestinal Fixation*

Case	Author	Year	Sex	Age	Symptoms and Signs	Result
1	Poley, E.; Bull. et mém. Soc. de chir. de Paris, 47: 1548, 1919	1919	F	14	Shoe size of 3 weeks, periodic attacks of vomiting of bile-stained material with epigastric pain; recently, epigastric pain after all meals; weak and malnourished; at operation, duodenum distended, fixed in kink on right side of vertebral column; common ileocolic mesentery with partial torsion of ascending colon	Well after release of kink in duodenum and colectomy
2	Denzer 37	1922	..	New-born	Delivery by cesarean section because of toxemia of pregnancy in eighth month; vomited all food since birth; death on twenty-sixth day; vomitus had been persistent and bile-stained; stools at first yellow, then watery and green; abdomen scaphoid; at autopsy, nonrotation, obstruction of duodenum caused by sharp duodeno-junal angle and squeezing of duodenum between ileum and cecum which was firmly bound down to posterior peritoneum at level of Treitz fossa	Death without operation
3	Thompson, J. W.; Bril. J. Surg., 16: 392, 1928	1928	F	23	Shoe size of 18; pain after eating; vomiting so that now able to retain only small quantities of food; at operation, nonrotation with duodenum obstructed by a kink at junction of first and second parts; transverse colon with long loop hanging into the pelvis	Well after duodenostomy, colocolostomy and resectoilepexy
4	Grant, J. W. G.; Surg., Gynec. & Obst., 41: 133, 1928	1928	F	37	For many years, fulness and flatulence following meals; for 6 weeks, persistent vomiting so that little or no food could be retained; at operation, nonrotation; duodenum obstructed by a double S-shaped kink firmly adherent to posterior abdominal wall; death after 3 days	Death after duodenostomy
5	Ladd 38	1932	F	New-born	Premature infant; onset 17 hours after birth; vomiting; persistent bile-stained vomitus since then; fulness in upper part of abdomen with visible peristalsis; lower part of abdomen scaphoid; roentgen examination showed markedly dilated duodenum; operation at age of 2 weeks; cecum fixed on left with obstruction of third portion of duodenum; death after 53 hours	Death after duodenostomy
6	Ladd 38	1932	F	11	Abdominal cramps and vomiting for 2 weeks; jaundice after fourth day; vomitus bile-stained; abdomen not distended at onset; before operation, epigastric distention and visible peristalsis; at operation, duodenum dilated to half the size of the stomach, obstructed by a nonrotated cecum firmly attached to the posterior abdominal wall over it	Well after cecum was freed from attachment across duodenum
7	Ladd 38	1932	M	2	Seen first at 1½ months with history of intermittent attacks of bilious vomiting for 1 month; epigastric distended with visible peristalsis; barium enema showed nonrotation; cecum 2 years later; had had periodic attacks of vomiting of bile-stained material; undernourished; dehydrated; upper part of abdomen distended; at operation, duodenum dilated; cecum in left upper part of abdomen with transverse colon crossing duodenum	Well after duodenostomy was freed

these structures and hold them in their normal position. The abdominal incision was closed in layers, catgut being used for the peritoneum and silk for the sheath of the rectus, subcutaneous tissues and skin.

Postoperative convalescence was uneventful. The patient remained in the hospital under an active antisyphilitic regimen until December 30, and since then has reported irregularly at the clinic for similar treatment. He has been completely relieved of all digestive disturbances. On April 7, 1933, roentgen examination after the barium meal showed that the stomach emptied rapidly. There was no dilatation of the duodenum, and barium passed through it without delay. A barium enema showed that the entire colon filled and lay in the normal position.

#### COMMENT

In both cases the clinical history and the physical findings were characteristic of a chronic duodenal obstruction. In both cases operation revealed a volvulus of the entire mesentery. The intestine was obstructed at the duodenojejunal junction, at which point the emerging segment of bowel looped around the entering segment and the twisted root of the mesentery. In each the emerging loop of bowel was not obstructed and the small bowel was collapsed. In both cases chronicity of symptoms, density of adhesions binding together entering and emerging segments of bowel and evidences of long-standing venous and lymphatic obstruction make it seem probable that the volvulus had been present since intra-uterine life or occurred shortly after birth. In case 1 normal rotation and fixation of the colon had taken place, though the duodenum remained on the right side of the vertebral column and the attachment of the root of the mesentery was inadequate. It is possible that volvulus took place during the process of reduction of the midgut loop in the tenth week of uterine life and that the colon subsequently rotated normally. It is more probable, however, that the deficient fixation of the mesenteric root predisposed to volvulus which was produced by the vigorous intestinal peristalsis incident to the first feedings. In case 2, the condition was exactly similar except that the cecum and ascending colon were also involved; deficient fixation of the common mesentery permitted formation of the volvulus. It is possible that the volvulus occurred at the age of 1 month; however, the evidences of long standing venous and lymphatic engorgement in the mesenteries of the midgut and the density of adhesions binding together the two loops of bowel involved in the twist suggest the possibility that the volvulus had been present since early intra-uterine life.

#### CASES IN WHICH ANOMALIES OF INTESTINAL ROTATION LED TO OBSTRUCTION OF THE INTESTINAL TRACT

Anomalies of intestinal rotation may exist without symptoms and be recognized only at anatomic dissection, at necropsy, on roentgen examination after a barium meal or incidentally at operation. Symptoms

appeared in only 13 of Dott's 48 cases collected in 1923. Incident to the present collection of 105 cases<sup>7</sup> with varying degrees of intestinal obstruction we have collected 70 cases of major defects in intestinal rotation which existed without symptoms. The first of these was reported in 1827 by Cruveilhier.<sup>8</sup>

Intestinal obstruction, either acute or chronic, may develop on the basis of anomalies of intestinal rotation because of (1) volvulus of the entire mesentery, (2) kinking or torsion of the ascending colon secondary to reversed rotation of the midgut loop or (3) kinking or pressure on the intestinal tract from abnormal fixation of the mesentery. In this report we have not included the cases with symptoms from an unduly mobile cecum or those of volvulus of the cecum, conditions which are undoubtedly secondary to a defect in the third stage of intestinal rotation but about which there is no confusion in the literature.

*Age and Sex.*—Of the 105 cases 55, or 52 per cent, were reported in new-born infants or in patients in whom symptoms had dated from a few days after birth. The latter group ranged in age from a few months to 27 years. Of the other 49 cases in which the age was given, 21 occurred in the third decade and from 3 to 7 in each of the other first six decades. Sixty-two per cent of the 97 patients whose sex was indicated were males.

*Etiology.*—Any departure from the orderly sequence of return of the intestine from the umbilical hernia into the abdomen is the reason given by Dott<sup>4</sup> for abnormalities of rotation. He believes that an unduly large umbilical orifice would exert no particular restraining influence on the cecum and thus permit a disorderly reduction. In cases of abnormal intestinal rotation reported by Hubner,<sup>9</sup> Hunter<sup>10</sup> and Reinhold<sup>11</sup> mesenteric cysts were also present, and it is quite possible that their presence in fetal life acted as obstructions to normal intestinal reduction. In the other cases no apparent cause for the anomaly could be found. The presence of other congenital anomalies has been noted

7. These cases comprise 103 collected from the literature and the 2 cases reported here.

8. Cruveilhier, E.: Disposition particulière de péritoine. Duodenum pourvu d'un mésentère: mésentère unique pour tous les intestins, *Bull. Soc. anat. de Paris* 2:202, 1827.

9. Hubner, Hans: Volvulus des gesamten Dünndarms und aufsteigenden nebst einem Teile des queren Dickdarms beim Mesenterium ileocolicum commune nach Exstirpation einer Mesenterialzyste, *Virchows Arch. f. path. Anat.* 201:427, 1910.

10. Hunter, J. I.: A Mesenteric Cyst of Jejeunal Origin Complicated by Retrojejeunal Position of the Transverse Colon, *Brit. M. J.* 2:800, 1922.

11. Reinhold, Paul: Kyste du mésentère compliqué de volvulus du grêle et du colon. Resection du kyste et de l'intestin grêle. Reduction du volvulus. Guérison, *Bull. et mém. Soc. de chir. de Paris* 58:523, 1932.

by Braeunig<sup>12</sup> whose patient also had a Meckel's diverticulum, by Grant<sup>13</sup> whose patient had a congenital absence of the shaft of the left radius, left thumb and first metacarpal, by Benham<sup>14</sup> whose patient had congenital cerebral diplegia, by Moritz<sup>15</sup> whose patient was a cretin, by Sauerbeck<sup>16</sup> whose patient had a patent interventricular septum and by Sencert<sup>17</sup> whose patient had an imperforate anus.

Contributory causes for the development of volvulus have been attributed to violent physical exertion, blows on the abdomen, exposure to extremes of temperature, operative manipulation, tumors, adhesions, starvation, constipation, vigorous cathartics and overeating. Any of these factors may have a bearing on the production of perversions in intestinal peristalsis which are probably most often the cause of the development of a volvulus. In volvulus neonatorum, of which there were 55 cases in this series, symptoms dated from the first few days of life and were probably initiated by the peristaltic efforts of the intestinal tract incident to the first food taken. In 2 cases (Radaeli<sup>18</sup> and Donald<sup>19</sup>) volvulus of the entire mesentery complicated pregnancy, while in 3 cases (Hubner,<sup>9</sup> Hausmann<sup>20</sup> and Hamann<sup>21</sup>) it occurred as a postoperative complication.

*Volvulus of the Entire Mesentery.*—This is the most common cause of intestinal obstruction secondary to anomalies of intestinal rotation and accounted for 88, or 83 per cent, of the 105 cases. If the condition of nonrotation and absence of intestinal fixation is present the suspension of the entire midgut from the narrow pedicle at the origin of the superior mesenteric artery may permit the development of a volvulus

12. Braeunig, Karl: *Volvulus des Dünndarms und Colon ascendens bei Hemmungsmißbildung des Darms*, Deutsche Ztschr. f. Chir. **186**:284, 1924.

13. Grant, J. W. G.: *Case of Non-Rotation of the Intestine*, Brit. J. Surg. **18**:166, 1930.

14. Benham, H. W.: *An Unusual Case of Volvulus*, Lancet **2**:340, 1932.

15. Moritz, A. R.: *Mesenterium Commune with Intestinal Obstruction*, Am. J. Path. **8**:735, 1932.

16. Sauerbeck, Ernst: *Ueber Entwicklungshemmung des Mesenteriums und abnorme Lageverhältnisse des Darms, insbesondere des Dickdarms*, Arch. f. klin. Chir. **89**:873, 1909.

17. Sencert: *Cas d'arrêt de torsion de l'intestin*, Compt. rend. Soc. de biol. **58**:325, 1905.

18. Radaeli, Guilio: *Sopra un caso di ileo in gravidanza da volvulo del tenue, del cieco e del colon ascendente*, Ann. di ostet. e ginec. **50**:1085, 1928.

19. Donald, Charles: *Volvulus of Small Gut, Caecum and Ascending Colon Associated with Congenital Reversed Rotation of Intestine and with Pregnancy*, Brit. J. Surg. **15**:269, 1927.

20. Hausmann, L.: *Beiträge zu den Lageanomalien des Darmes: Mesenterium Commune, Postposition des Dickdarms (Col. Transversum) hinter dem Dünndarms (Duodenum) Achsendrehung*, Zentralbl. f. Chir. **27**:19, 1900.

21. Hamann, C. A.: *Faulty Rotation of the Intestine*, Ann. Surg. **76**:491, 1922.

of the entire small intestine, cecum and ascending and right half of the transverse colon. Such a volvulus of the entire midgut was present in 23 of the 88 cases of total volvulus. On the other hand, the presence of malrotation or of nonrotation with deficient fixation may predispose to formation of a volvulus of the entire small intestine, such as occurred in 24 of the 88 cases, or of the entire small intestine, cecum and ascending colon, such as occurred in 41 of the cases.

Two degrees of volvulus of the entire mesentery may be recognized pathologically depending on the tightness of the torsion and on the degree of vascular occlusion. If the twist obstructs both the entering and the emerging segment of bowel and the blood supply is obstructed, the entire involved intestine becomes enormously distended and gangrenous. The pathologic picture in such a condition is the usual one of acute intestinal obstruction with strangulation. On the other hand, if the volvulus is less tight, as is more frequently the case, the third part of the duodenum is obstructed at the point where it winds around the mesenteric root, while the colon, which is less fixed, is not occluded. Since the involved bowel has a free exit below through the colon it remains collapsed, while the stomach and duodenum become enormously distended. The picture is thus entirely one of duodenal obstruction without any of the usual features of volvulus. If the vascular occlusion is acute there may be a bloody peritoneal fluid, and blood may be extravasated into the bowel and subsequently passed by rectum. If the volvulus is chronic, as in both of our cases, evidences of long-standing venous and lymphatic obstruction will be apparent. In such a case the mesentery of the midgut will be thickened, and in it may be found enlarged lymph nodes, dilated lymphatic vessels and veins as large as one's finger.

The direction of rotation was clockwise in 56, or 70 per cent. of the 79 cases of volvulus in which it was indicated. Torsions varying from 120 degrees to four complete turns were encountered. Tightness of the torsion rather than the number of turns determines the severity of the symptoms. Benham's case<sup>14</sup> was seen in collapse ten hours after the onset of symptoms with a torsion of 180 degrees while in the case of Kuljazbo and Koreski,<sup>22</sup> operation was performed on the fifth day of symptoms, and four complete turns of the mesentery were found.

Clinically two entirely different forms of volvulus of the entire mesentery may be encountered. In the one the picture is entirely that of acute or chronic obstruction to the duodenum without any of the usual signs of volvulus. In the other the picture is typical of volvulus with acute intestinal obstruction with or without evidence of strangulation.

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22. Kuljazbo and Koreski, quoted by Brenner.<sup>43</sup>



*Volvulus with Symptoms of Duodenal Occlusion.*—This is the more common condition which follows volvulus of the entire intestinal tract and was present in 52 (70 per cent) of the 75 cases in which the description was complete enough for analysis. The obstruction may be partial, complete or intermittent. Usually symptoms are chronic, frequently beginning within a few days after birth and consist of recurring attacks of abdominal pain, vomiting and constipation without abdominal distention.

This condition has been reported in 32 new-born infants. No intestinal abnormality is apparent at birth. The first feedings are taken normally. Meconium and in some cases normal stools are passed. Vomiting, constipation and abdominal pain usually manifest themselves about the third or fourth day. Vomiting is persistent and projectile. It occurs usually from twenty to thirty minutes after feedings (later than in congenital pyloric stenosis) and in cases reported by Dott,<sup>4</sup> Durante<sup>23</sup> and Oberling<sup>24</sup> the vomitus contained blood. Since the obstruction is below the ampulla in the duodenum, the vomitus always contains bile. Epigastric distention and frequently visible gastric peristalsis are present, while the lower part of the abdomen remains scaphoid. If vascular obstruction accompanies the volvulus, blood-stained fluid may be passed by rectum as in cases reported by Pinkerton,<sup>25</sup> Blecher,<sup>26</sup> Durante,<sup>23</sup> Lawson,<sup>27</sup> Michaelis<sup>28</sup> and Dott<sup>29</sup> (2 cases). In the case of Charlsey and Richardson<sup>30</sup> blood leaked continuously and in large quantity from the rectum. Acidosis, dehydration and demineralization of the blood may be extreme and may cause the child's death. In cases in which the volvulus has progressed to complete strangulation death occurs much more promptly and is probably hastened by the rapid loss of blood into the intestinal tract.

23. Durante, G.: Occlusions congénitales de l'intestin, *Bull. Soc. anat. de Paris* 6:593, 1901.

24. Oberling, Charles: Trois cas de volvulus par torsion du mésentère commun persistant, *Rev. franç. de pédiat.* 3:96, 1927.

25. Pinkerton, C. C.: Volvulus Neonatorum Due to Anomalous Intestinal Rotation, *Ann. Surg.* 86:633, 1927.

26. Blecher: Ueber Ileus bedingt durch selteneren Formen von Volvulus, *Deutsche Ztschr. f. Chir.* 64:48, 1902.

27. Lawson, T. C.: Volvulus of the Entire Small Intestine, *California & West. Med.* 26:189, 1927.

28. Michaelis, P.: Achsendrehung des Dünndarms und des Colon ascendens bei einem Neugeborenen, *Wien. klin. Rundschau* 27:662, 1913.

29. (a) Dott, N. M.: Volvulus Neonatorum, *Brit. M. J.* 1:230, 1927; (b) footnote 4.

30. Charlsey, G. W., and Richardson, G.: A Case of Volvulus Neonatorum, *Brit. M. J.* 1:494, 1928.

If the condition is less acute the child may escape death in early infancy but will remain susceptible to repeated attacks of partial duodenal obstruction throughout the remainder of his life. Seventeen such cases in an age group of from 3 to 27 years are included in this series. These patients had a history, dating from birth, of repeated attacks of abdominal pain, vomiting and constipation but without abdominal distention. The pain is usually the typical cramp of intestinal colic, though it may manifest itself only as an epigastric discomfort. It is frequently precipitated by meals and usually relieved by vomiting. Vomiting is forceful and copious; the vomitus is bile-stained and frequently contains food residue of meals eaten many hours previously. The upper part of the abdomen is distended; the lower, scaphoid, and visible gastric peristalsis may be evident during attacks. Constipation is generally present although occasionally small stools of normal fecal material are passed during attacks. Blood in the vomitus or in the stools did not occur in any of the cases. Pathetic degrees of emaciation and dehydration often occur. Rixford<sup>31</sup> reports the case of a child aged 5 years who had never been able to eat a full meal without initiating an attack. Because of the weakness of starvation this patient could be out of bed only a few hours each day.

Roentgen examination of the gastro-intestinal tract reveals a partial obstruction in the duodenum, usually in the third portion, with enlargement of the duodenum and stomach and prolonged retention of barium in these organs (fig. 11). The characteristic finding, however, and the one on which the roentgenologist may frequently establish a diagnosis of an anomaly in intestinal rotation, is the presence of the entire duodenum on the right side of the vertebral column. The normal curve of the duodenum to the left across the midline and under the stomach is lost. This condition was present in case 1. The visualization of the colon entirely on the left side of the abdomen is indicative of an abnormality of rotation. However, in these cases sufficient barium to fill the colon satisfactorily rarely passes the duodenal obstruction. The entire colon, if not involved in the volvulus, will be filled by a barium enema, and "left-sided colon," if present, is easily detected. At other times, as in case 2, there may be an obstruction to the passage of barium by an enema beyond the site of the volvulus in the right half of the colon.

*Volvulus with Symptoms of Acute Intestinal Obstruction.*—This condition was present in 23 of the cases of total volvulus. The symptomatology is not unlike that of acute intestinal obstruction from any cause, except that the vomitus is rarely fecal. The usual picture is that of

31. Rixford, E.: Failure of Primary Rotation of the Intestine (Left-Sided Colon) in Relation to Intestinal Obstruction, *Ann. Surg.* 72:114, 1920.

sudden onset of acute intestinal colic with vomiting, obstipation and abdominal distention. Symptoms of strangulation with death in collapse as early as six hours after the onset may be present (Helmsmüller<sup>32</sup>). In Köhler's<sup>33</sup> case seen in collapse two hours after onset the condition was mistaken for a ruptured ectopic pregnancy. A history of one or two similar attacks in a milder form is sometimes given; usually, however, these patients have enjoyed excellent health and have been singularly free from abdominal discomfort. It is probable that before operation this condition cannot be distinguished from any other form of acute intestinal obstruction.

*Reversed Rotation with Acute Obstruction of the Colon.*—In reversed rotation the transverse colon comes to lie under the duodenum and superior mesenteric artery and may become trapped in this position by the acquired attachment of the root of the mesentery (fig. 10). Obstruction to the transverse colon at the point where it pierces the root of the mesentery may take place by torsion or kinking of the mobile cecum and ascending colon. Thirteen cases of reversed rotation have been collected. In 3 (Hausmann,<sup>20</sup> Braeunig<sup>12</sup> and Donald<sup>19</sup>) attachment of the mesenteric root was inadequate, and volvulus of the entire mesentery took place. In the other 10 cases (table 2) obstruction occurred in the middle of the transverse colon secondary to kinking or torsion of the right half of the colon which retained its primitive mesentery.

Symptoms of this condition are not unlike those of acute obstruction of the colon from any cause. Frequently a history of repeated milder attacks in the past may be elicited, or the condition may exist without symptoms for years, as in the case of Dott<sup>4</sup> whose patient, 68 years of age, was seen in his second attack. Peigneaux and Fruchard<sup>34</sup> reported the case of a 15 year old girl with an associated chronic duodenal obstruction, symptoms of which had been present since birth. In the cases of Hunter<sup>10</sup> and Harvey<sup>35</sup> the condition caused death in the new-born. On abdominal examination the outline of the tremendously dilated cecum and ascending colon may be made out. It is improbable that before operation this condition can be distinguished from any other type of acute obstruction of the colon. However,

32. Helmsmüller: Ein Fall von Achsendrehung des gesamten Dünndarms und des aufsteigenden Dickdarms, Thesis, Kiel, 1898; quoted by Blecher.<sup>26</sup>

33. Köhler, H.: Volvulus des Zokokolons und des gesamten Dünndarms, Deutsche med. Wchnschr. 44:519, 1918.

34. Peigneaux, and Fruchard, Henri: Troubles digestifs graves chez une jeune fille de quinze ans en relation avec des malformations portant sur le duodenum et le colon droit, Bull. et mém. Soc. de chir. de Paris 56:335, 1930.

35. Harvey, Frank: Intestinal Obstruction in a Child of Three Days Due to Abnormal Intestinal Rotation, Brit. J. Surg. 14:187, 1926.

should it be encountered at laparotomy, a knowledge of the possibility of such a condition is of great value.

*Obstruction from Abnormal Intestinal Fixation.*—Seven cases of obstruction of the duodenum caused by abnormal fixation of the intestinal tract incident to anomalies of intestinal rotation have been collected (table 3). In 5, fixation of the duodenum in abnormal kinks caused the obstruction. In Ladd's<sup>36</sup> case the duodenum was occluded by the firm fixation of a nonrotated and abnormally fixed cecum across it, while in Denzer's<sup>37</sup> case the duodenum was tightly squeezed between the nonrotated and abnormally fixed cecum and the terminal ileum.

In addition to these 7 cases of duodenal obstruction Woolsey<sup>38</sup> reported 2 cases with symptoms of indigestion and flatulence in which the nonrotated cecum was firmly fixed to the gallbladder, pylorus and duodenum. These symptoms were probably caused by dysfunction of the gallbladder rather than by duodenal obstruction. Brouet and Caroli<sup>39</sup> reported the case of a boy aged 17 who had had frequent attacks of abdominal pain and in whom at operation nonrotation of the midgut with adhesions between the ascending colon and the right loop of the transverse colon were found. Recovery followed right colectomy and ileocolostomy. Hecker<sup>40</sup> reported the case of a woman aged 52 who for a year had suffered from recurring abdominal pains and in whom at operation nonrotation with adhesions between the colon and the small intestine were found. In 1927 Vaughn<sup>41</sup> reported 5 cases in which malformation of the mesentery accounted for a variety of abdominal symptoms; in 1930 Grant<sup>13</sup> reported the case of a man aged 32 who had had recurring attacks of abdominal pain and in whom nonrotation of the midgut loop without volvulus or abnormal fixation was found.

Symptoms and clinical findings in the patients with duodenal occlusion secondary to abnormal intestinal fixation are the same in every respect as those of duodenal obstruction from volvulus. In the second group with symptoms due to unusual position and fixation of the intestines Vaughn<sup>41</sup> emphasized the "unusualness" of the pain, the

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36. Ladd, W. E.: Congenital Obstructions of the Duodenum in Children, New England J. Med. **206**:277, 1932.

37. Denzer, B. S.: Congenital Duodenal Obstruction; Malrotation of the Intestine, Am. J. Dis. Child. **24**:534 (Dec.) 1922.

38. Woolsey, R. A.: Non-Rotation of the Midgut, Internat. J. Med. & Surg. **40**:314, 1927.

39. Brouet, and Caroli: Arrêt de torsion de l'intestin, Bull. et mém. Soc. de chir. de Paris **54**:366, 1930.

40. Hecker, Paul; Grünwald, E., and Kuhlmann, C. J.: Les anomalies congénitales de forme et de position du gros intestin et leur importance chirurgicale, Rev. de chir., Paris **64**:661, 1926.

41. Vaughn, George E.: Congenital Malformations of the Mesentery: A Clinical Entity, Brit. J. Surg. **15**:438, 1927.

"emptiness" of the right iliac fossa as a result of the absence of the cecum from its normal position, and the roentgen findings after the barium meal as the important factors which enabled him to make the correct preoperative diagnosis in 4 of his 5 cases.

*Diagnosis.*—It is improbable that a correct preoperative diagnosis of volvulus of the entire mesentery causing acute intestinal obstruction or reversed rotation with acute obstruction to the colon can be made unless an anomaly of intestinal rotation has been previously recognized in the patient. However, the condition should be recognized before operation in new-born infants, children and young adults who show symptoms of acute or chronic duodenal obstruction without evidence of volvulus. The differential diagnosis is to be made from hypertrophic pyloric stenosis, congenital atresia or stenosis of the intestine, intussusception, volvulus of a limited portion of the intestine, or intestinal obstruction from tumors or from anomalous intraperitoneal bands.

The persistent vomiting following feedings, the epigastric distention and the visible gastric peristalsis in the new-born may cause a confusion in diagnosis with pyloric stenosis. In total volvulus, however, the vomiting is always bile-stained as the obstruction is below the ampulla of Vater; symptoms usually begin earlier in life, and the vomiting occurs at a longer interval after feedings. Congenital atresia of the duodenum may be distinguished by the fact that in this condition vomiting begins immediately after birth and meconium is not passed by rectum. Congenital stenosis of the lower duodenum in which the obstruction is partial closely simulates the partial duodenal obstruction of total volvulus. In the former condition symptoms date from birth, while in the latter they date only from the onset of the volvulus. Roentgenologic findings of a duodenum wholly on the right of the vertebral column is the greatest aid in differentiating the two conditions. In congenital stenosis of the intestine and in the acquired intestinal obstructions from tumors, peritoneal bands, intussusception and volvulus of a limited segment of the intestine differentiating features are found in the generalized abdominal distention and in the vomitus which soon becomes feculent. These symptoms are present in all the latter conditions but not in the duodenal obstruction resulting from volvulus of the entire mesentery.

*Treatment.*—Operative treatment offers the only hope of cure in patients with obstruction to the duodenum or lower intestinal tract secondary to anomalies of intestinal rotation. In the group with symptoms of acute intestinal obstruction, whether in the duodenum or lower, early operation is imperative, for in these cases as in any acute intestinal obstruction the mortality rate mounts rapidly with each hour of delay. In the group with chronic duodenal obstruction with intermittent acute attacks a more leisurely preparation for operation may be

pursued. However, in this group nonoperative treatment is not justified, as evidenced by the fact that in our series 8 of the 17 patients with this condition died without operation during acute exacerbations of the attacks from which they had suffered all their lives.

Volvulus of the entire mesentery may be easily overlooked at operation if the condition is not kept in mind or if adequate exploration is not made. The condition may be suspected if the right half of the colon is not found in its normal position or if on palpation a firm cord representing the twisted root of the mesentery can be felt at the site of origin of the superior mesenteric artery. Adequate exposure with visualization of this area usually makes the diagnosis obvious, although evisceration may be necessary before the condition becomes clear. Detorsion of the volvulus after complete evisceration of the involved intestine with replacement of the viscera in their normal position is the ideal operative procedure. Duodenojejunostomy alone has been performed successfully in one case (Lee<sup>42</sup>). Because of the vascular and lymphatic obstruction which inevitably accompanies volvulus and because of the possibility that this obstruction may become complete we do not consider this procedure advisable. If, after detorsion, the condition of the patient permits, some form of fixation of the cecum and ascending colon in their normal position is advisable. In cases reported by Ladd<sup>36</sup> and Brenner<sup>43</sup> recurrence of the volvulus occurred one and nine months, respectively, after the original operation in which simple detorsion had been performed. In each case this necessitated a second operation with detorsion and fixation of the ascending colon. In the 2 cases reported by Heyman<sup>44</sup> a tendency for the volvulus to recur while the abdomen remained open was noted, and in each colopexy was found necessary to maintain reduction of the volvulus. If adhesions bind together entering and emerging loops of bowel involved in the volvulus, as occurred in both of our cases, these adhesions must be carefully and thoroughly freed before reduction can be maintained. It is probable that the secondary adhesions which form about the raw surfaces thus produced will prevent recurrence of the volvulus, and on such an assumption colopexy was not performed in either of our cases. In the 30 patients with total volvulus who survived operation the procedure was as follows: simple detorsion, 19; detorsion and fixation of the cecum and ascending colon, 9; duodenojejunostomy, 1, and detorsion and duodenojejunostomy, 1.

42. Lee, A. E., and Nye, L. J. J.: Chronic Duodenal Obstruction Due to Non-Rotation of the Midgut Loop with Superadded Volvulus, *M. J. Australia* 2:18, 1932.

43. Brenner, E. C.: Total Volvulus, *Am. J. Surg.* 16:34, 1932.

44. Heyman, E.: Volvulus des gesamten Dünndarms, *Deutsche med. Wchnschr.* 48:725, 1922.

Acute obstruction to the colon secondary to reversed rotation may be recognized at operation by the enormous dilatation of the mobile cecum and ascending colon, the distention ending abruptly at the point where the transverse colon passes under the duodenum. In our series only 2 of the 10 patients with this condition survived. One of these was treated by reduction of the kink in the colon and cecopexy (Serck-Hanssen<sup>45</sup>); the other, by lateral colocolostomy (Peigneaux and Fruchard<sup>34</sup>); complete relief of symptoms occurred in both cases. Either of these forms of treatment may be applied in the early cases, but in obstructions of long duration a temporary cecostomy after untwisting of the mobile cecum is probably the procedure of choice. This relieves the acute obstruction and also fixes the cecum in normal position so as to prevent a recurrence. In such condition it is impossible to replace the colon in its normal position.

In the case of duodenal obstruction caused by abnormal intestinal fixation, release of the obstruction by freeing the duodenum from its attachment to the parietal peritoneum is the procedure of choice. Duodenojejunostomy may be performed as an alternative. Of the 4 patients with this condition who survived operation 1 had had a duodenojejunostomy, while the other 3 had had simple release of the abnormal duodenal attachment.

*Prognosis.*—The prognosis in obstruction to the intestinal tract subsequent to anomalies of rotation depends on the level, the degree of obstruction, the presence or absence of strangulation and the time of operation after the onset of symptoms. All the patients not operated on died. Of the 32 patients with volvulus neonatorum reported within the first months of life 16 died without operation, and of the 16 operated on 8, or 50 per cent, recovered. Of the 17 patients in an age group between 3 and 27 years with volvulus and with symptoms of duodenal obstruction dating from birth, 8 died without operation during acute exacerbation of their attacks. Eight, or 88 per cent, of the 9 operated on survived and were cured. Of the 39 adults in whom the condition occurred, 8 died without operation, and of the remaining 31 operated on 14, or 45 per cent, recovered. In the group of 88 cases of volvulus of the entire mesentery 32 patients died without operation, and of 56 subjected to operation 30, or 53 per cent, survived and were cured. Three of the 10 patients with reversed rotation and obstruction of the colon died without operation and only 2, or 28 per cent of the 7 operated on, survived. Of the 7 patients with duodenal obstruction caused by abnormal intestinal fixation 1 died without operation and 4, or 66 per cent, of the 6 operated on survived and were cured. In the entire series

45. Serck-Hanssen, Trygve: Retroposition Coli, Volvulus Coeci, *Med. Rev.*, Bergen 43:557, 1926.

of 105 cases 36 patients died without operation, while 36, or 52 per cent. of the 69 subjected to operation survived and were relieved of all symptoms.

#### SUMMARY

1. A precise knowledge of the possibilities of derangement of the intestinal tract incident to anomalies of intestinal rotation is essential.
2. The stages in normal intestinal rotation and the possibilities of abnormality in each are described.
3. Two cases of volvulus of the entire mesentery secondary to abnormalities of intestinal rotation with symptoms of chronic duodenal obstruction seen by us are presented in detail.
4. One hundred and five cases of intestinal obstruction incident to abnormalities of intestinal rotation are collected from the literature. Eighty-eight of these were caused by volvulus of the entire mesentery, 10 by obstruction to the transverse colon secondary to reversed rotation and 7 by obstruction of the duodenum by abnormal intestinal fixation.
5. Symptoms of acute intestinal obstruction may accompany volvulus of the entire mesentery. More often the picture is that of acute, chronic or intermittent obstruction of the duodenum below the ampulla without any of the usual evidences of volvulus.
6. Correct preoperative diagnosis of the cases causing duodenal obstruction should be made.
7. Operative treatment for each form of obstruction is considered.



# GENERAL SENSATIONS IN PEDUNCULATED FLAPS OF SKIN

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The fact that the sensations of touch, pain and temperature eventually return in skin grafts and in pedunculated flaps of skin<sup>1</sup> and subcutaneous tissue after transplantation has been known to surgeons for a long time, but so far as we are able to ascertain, no attempt has been made to find out what the early sensations are in pedunculated flaps and what relationship these sensations have to each other.

Several years ago, we began to gather from our clinical work in plastic surgery data which could eventually be analyzed and from which we hoped to obtain definite information as to these points. A large amount of material has been accumulated, and from this we have selected small groups of flaps of different types, which are typical and which indicate the results obtained.

It will be noted that the observations listed in this report deal entirely with pedunculated flaps and are largely for the purpose of determining the early relationship of the sensations of touch, pain and temperature. The majority of the observations were made quite early on flaps in which the transfer was delayed, such as tubed flaps, while other observations were made on flaps which were immediately transferred to fill the defect for which they were prepared. However, in some tubed flaps it was possible to make observations months after they were formed but still before their transplantation.

The regeneration of sensations in skin grafts and in transplanted flaps in which the pedicles have been divided has been considered in another report.<sup>2</sup>

Since the work of Head and his associates<sup>2a</sup> the subject of the general sensations in the skin has received much attention, and controversies have arisen about the relationship of the sensations to each other after

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1. A flap of skin is an area of skin and subcutaneous tissue attached at some portion of its periphery or base by a pedicle or pedicles, through which it receives its blood supply and which can be shifted only so far as the pedicle allows.

2. Davis, John Staige, and Kitlowski, E. A.: Regeneration of Nerves in Skin Grafts and Skin Flaps, *Am. J. Surg.* **24**:501 (May) 1934.

2a. Head, Henry, and others: *Studies in Neurology*, New York, Oxford University Press, 1920, vol. 1.

nerves have been cut and sutured. Trotter and Davies,<sup>3</sup> Boring<sup>4</sup> and Cobb<sup>5</sup> question the disassociation theory of Head and believe that the region of sensory loss is approximately the same for all forms of sensibility. The whole subject has been ably summarized by Lee<sup>6</sup> in his report "The Regeneration of Nervous Tissue." Like Trotter and Davies and Boring, we have secured results similar to Head, using the same methods, which all agree are very satisfactory clinically. A brief explanation of the different types of sensibilities, as postulated by Head and his associates and by Lickley,<sup>7</sup> is as follows:

Epicritic sensibility refers to the finely graded and definitely localized sensations of tactile impressions and mild degrees of heat and cold. This sensibility exists in the skin only.

Protopathic sensibility refers to the sensations of pain and extreme degrees of heat and cold. This sensibility is the more primitive, existing in the skin and in the viscera, and acts as a defensive agency against pathologic changes in the tissues.

A third system of general sensations existing at the periphery, known as the deep set, arising from the muscles, joints, etc., conveys the sensibilities of position, deep pressure and pain and movements in the muscles, joints and tendons.

These sensations may be stimulated in groups or individually, depending on the type and intensity of the stimuli. A very light touch which does not depress the skin or disturb the hair on the skin is reported by the epicritic system. If the touch is pressure which causes a depression in the surface of the skin, it is reported by the epicritic system which definitely localizes it and also by the deep system reporting pressure. If the pressure is more severe, causing pain, it is reported by the epicritic system which localizes the spot and by the deep system which reports pain. If the epicritic system is eliminated by some cause, the pressure is reported as coming grossly from a certain region, but without accurate localization of the exact area. If there is gentle touch only and the epicritic system is not functioning, there will be no consciousness of touch.

The sensation of pain as elicited by the prick of a sharp pointed instrument, as a needle or pin, is reported by the protopathic system.

3. Trotter, W., and Davies, H. M.: Experimental Studies in the Innervation of the Skin, *J. Physiol.* **38**:134, 1909.

4. Boring, E. G.: Cutaneous Sensation After Nerve Divisions, *Quart. J. Exper. Physiol.* **10**:1, 1916.

5. Cobb, S.: Cutaneous Sensibility in Cases of Peripheral Nerve Injury, *Arch. Neurol. & Psychiat.* **2**:505 (Nov.) 1919.

6. Lee, F. C.: The Regeneration of Nervous Tissue, *Physiol. Rev.* **9**:575 (Oct.) 1929.

7. Lickley, J. D.: The Nervous System, New York, Longmans, Green & Co., 1931.

The epicritic system accurately localizes the point because the stimulus arouses this system when it touches the skin before causing pain. The deep system is also brought into action by the pressure of the instrument, and if the stimulus is very severe that system also reports pain. Absence of the epicritic system causes pain to be reported in a general region without accurate information about the exact area. If both the epicritic and the protopathic systems are not functioning the prick is reported as pressure unless the stimulus is very intense, when it is recognized as pain. This stimulus must, however, be so intense as to injure tissue before it is recognized. Thus an area lacking the epicritic and protopathic sensations can be incised, the patient feeling pressure only.

#### METHODS OF TESTING

In view of the difficulties necessarily encountered in testing the flaps, we determined to limit our investigations to sensations of touch, pain and temperature. In order to test for both the epicritic and the protopathic systems as defined by Head and others,<sup>2</sup> we limited our test of touch to epicritic touch and used the prick test to elicit pain as an expression of the protopathic system. The tests of temperature were made with extremes of heat and cold and are an expression of the protopathic system.

Before beginning the tests every effort was made to obtain the cooperation and interest of the patient. All the patients, as will be noted in the time after operation in which the test was performed, had recently undergone some more or less unpleasant operative experience, and it was necessary to assure them that these tests would not cause further pain or be distressing to them in any way. The tests were carefully explained and demonstrated in full view of the patient so that each one would understand what was desired. The patient was then placed in the most comfortable position possible and asked to report with a simple "yes" or "no" concerning the sensation. The tests were carried out in a quiet room, and the patient was not permitted to observe the actions of the operator, so that the replies would not be influenced by what was seen. If a patient showed a tendency to tire or to permit his attention to wander, the test was stopped and resumed after a short period of rest. The tests were made by one of us (E. A. K.) in order to eliminate any difference in personal error.

Light touch was tested by the use of a bit of cotton wrapped around the end of a toothpick and frayed so that wisps of the cotton alone touched the skin. The sensation of touch can be elicited in several ways: by touching the skin, by pressing on the skin and by touching the hairs of the skin. Any pressure, however slight, which causes a depression in the surface of the skin, produces a sensation of touch which is reported through the protopathic system. A more intense pressure elicits an additional response from the system of deep sensibility located in the tissues underlying the skin. Touch is also reported by sensory nerve organs at the bases of hairs, believed to belong to the protopathic system, which are stimulated by any movement of the hairs. The sensation of light touch not conveyed by pressure or movement of the hairs is a finer tactile impression which is carried by the epicritic system. It was this light touch which we tested. The wisps of cotton were applied

gently to the skin, and the patient was asked to report whether he felt them or not. As a rule the areas used for securing flaps were not hairy and, in addition, had been shaved before operation so that the hairs were not a factor in our tests. Inasmuch as we were interested in the gross data only, tests with von Frey<sup>8</sup> hairs were not used. The wisps of cotton were gently applied to the skin until a point was reached at which the patient did not feel the touch. This point was then marked with 5 per cent solution of brilliant green in alcohol applied with the point of a toothpick. The process was repeated until the whole flap had been tested. The points were then joined, and the line so formed indicated the limit of the sensation of touch.

Sensibility to pain was tested by pricking the skin with a sharp pointed pin or needle. The patient was first instructed to distinguish between prick and touch. No effort was made in these tests to determine the intensity of the pain, and we were careful to make sure that the patient could distinguish between sharpness and soreness. The pressure applied was so slight that the sensation of pain which is elicited by pressure was not produced in our tests. The skin was pricked gently over the entire area, and the points at which pain was no longer felt were marked. This procedure was repeated a number of times over the same part to make sure that no pain spot was missed.

The sensibility to heat and cold was tested by means of ordinary test tubes containing cracked ice or hot water. This method is useful in securing only the coarsest observations since it is impossible to record the exact temperature as the glass will be of a different temperature from the contents when it comes in contact with the skin. The extremes of temperature gave information about the protopathic system. We did not test with moderate degrees of heat or cold, sensations which are conveyed by the epicritic system. The test tubes were placed on the skin and moved from spot to spot until the patient did not feel either heat or cold. The test was performed first with the cold and then with the hot tube. We did not attempt to separate the two sensations in our tracings. The end of a test tube is rather large, so that the findings could not be very accurate, and we simply noted their location in regard to the limits of the sensations of light touch and pain.

After the sensations had been tested and their limits marked, a piece of perforated cellosilk was placed over or around the flap, and the lines traced on it with brilliant green. The tracings were then transferred to sheets of paper and labeled.

#### OBSERVATIONS

We have grouped the data secured into three divisions depending on the types of flaps tested: (1) single-pedicled flaps, (2) double-pedicled flaps and (3) tubed flaps.

*Single-Pedicled Flaps.*—These flaps are tongue-like areas of skin and subcutaneous tissue which are raised and have a single pedicle. They either were transferred immediately or were sutured back and the transfer was delayed.

The flaps raised in the temporal region were in an area innervated by the trigeminal nerve. They were usually formed over the temporal

8. von Frey, M.: Untersuchungen über die Sinnesfunctionen der menschlichen Haut, Abhandl. d. math.-phys. Cl. d. k. sächs. Gesellsch. d. Wissensch. 23:214, 1896.

artery in the direction it follows on the head. The innervation of the upper portion of the flap was cut across so that there was very little sensation left.

The flaps on the abdominal wall were raised with the pedicles more or less in a line with the courses of the nerves so that the innervation extended down the flaps almost to the ends, if they were short. In cases 5 and 6, the flaps were longer and more narrow in proportion, so that the innervation was destroyed. In case 8, the flap was wider than it was long and sensations were present over seven tenths of its length even though it had been raised across its innervation.

Summary: All the single-pedicled flaps were utilized either immediately or within two weeks after their formation so that regeneration of sensations was not found in any of them.

TABLE 1.—*Single-Pedicled Flaps*

	Case	Age	Sex	Date of Formation	Length of Flap, Cm.	Width of Flap, Cm.	Time, Days	Distance from Pedicle*	
								Prick	Touch
Flaps raised in the temporal region	1	49	M	2/13/30	8.2	2.2	12	3.0	2.6
	2	60	M	4/20/23	8.0	2.0	10	2.1	1.5
Flaps raised on the abdominal wall	3	46	M	1/ 4/27	6.0	3.4	13	4.1	3.6
	4	34	M	1/10/28	6.0	4.0	14	5.0	4.4
	5	20	M	1/25/23	12.0	3.2	4	4.0	3.5
	6	22	M	6/22/27	10.0	5.4	10	4.5	4.0
	7	32	M	3/23/27	8.5	3.8	13	6.0	5.3
	8	57	M	11/21/23	10.5	12.0	7	7.2	4.6
	9	44	M	2/14/33	8.0	5.0	9	3.0	2.5

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

The extent of the loss of sensations depended on the extent to which destruction of the nerves occurred. If only the smaller branches of the peripheral nerves were traumatized, the destruction of sensations was lessened. If a flap was cut broad and short the nerve branches in the major portion of the flap were not injured, and the sensations were present over a greater area than if a very narrow and long flap was formed. The temperature sensations were found between the lines of touch and pain.

*Double-Pedicled Flaps.*—These flaps are areas of skin and subcutaneous tissue which are raised between two parallel incisions and which have a pedicle at each end continuous with the skin. The flaps were either sutured back into their original beds to be used later, and at the proper time after one pedicle had been divided were shifted and sutured into their new position, or they were transferred immediately, being used as a "gauntlet." In order to simplify the neurologic survey the data on double-pedicled flaps are grouped into three tables depending on the anatomic region in which the flaps were raised.

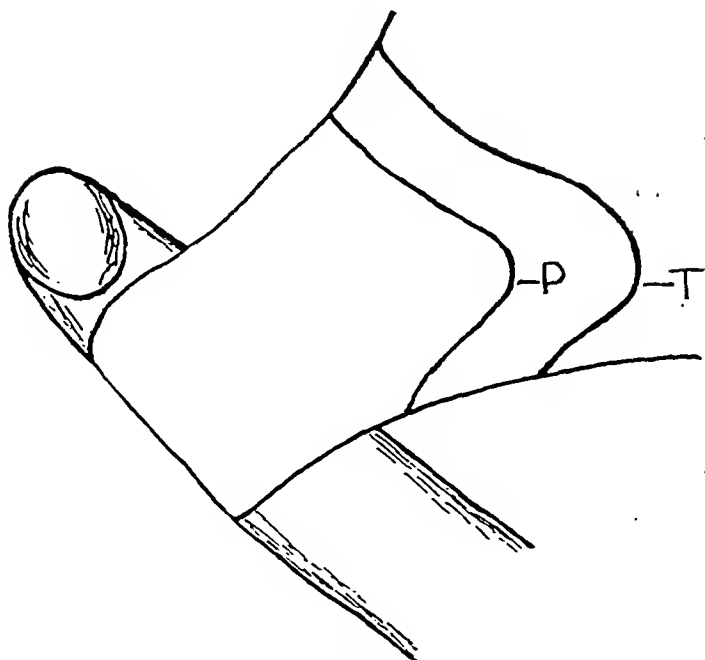


Fig. 1 (case 3, table 1).—A single-pedicled flap raised on the abdominal wall and immediately transferred to the finger. The curved line *P* indicates the limit of prick on the flap. The curved line *T* indicates the limit of epicritic touch. The tests were performed on the thirteenth day. The drawing shows the actual size of the flap and of the finger.

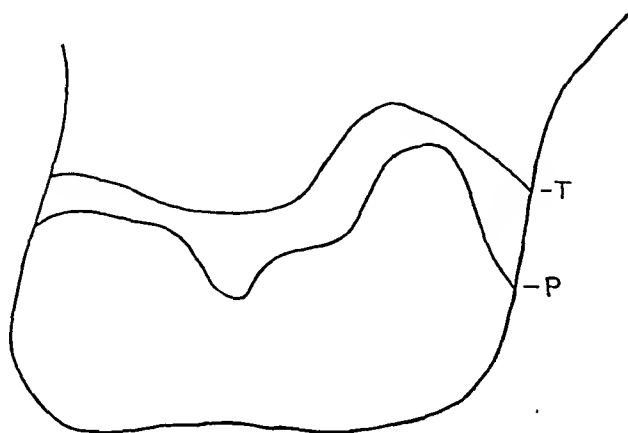


Fig. 2 (case 8, table 1).—The outside line shows the delayed transfer flap with a single pedicle formed on the abdominal wall. The curved line *P* shows the limit of prick sensation. The curved line *T* shows the limit of light touch. The tests were made seven days after the flap was raised and replaced in its own bed but before it was transferred to the hand for which it was planned. Note the types of curves developed in the tests. The illustration is one-half the actual size of the flap.

The flaps raised on the forehead were made from the root of the nose obliquely toward the hair-line. This area is innervated by the trigeminal nerve, which is sensory. In case 1 the flap was raised in the temporal region from in front of the ear toward the hair-line. With that exception all the flaps reported on in table 2 were supplied by both trigeminal nerves. All these flaps were sutured back after being formed; in other words, the transfer was delayed.

"Upper end" indicates the end of the flap near the hair-line and "lower end" refers to the end near the nose. In case 1, the upper end was on the forehead and the lower end was in front of the ear.

TABLE 2.—*Double-Pedicle Flaps Raised on the Forehead*

Case	Age	Sex	Date of Formation	Length of Flap, Cm.	Width of Flap, Cm.	Time, Days	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	25	M	12/15/30	9.5	2.5	13	0.5	0.0	1.5	1.0
2	34	M	3/21/28	7.5	2.5	8	1.0	0.5	1.4	1.1
3	48	F	5/16/28	7.2	2.4	7	0.8	0.2	1.5	1.0
4	55	M	11/28/32	7.7	2.4	10	1.0	0.5	0.5	0.0
5	30	F	12/31/27	6.7	2.6	10	0.8	0.4	1.2	0.7
6	30	M	4/ 6/31	7.3	2.4	12	0.6	0.2	1.1	0.4

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

TABLE 3.—*Double-Pedicle Flaps Raised on the Abdominal Wall.*

Case	Age	Sex	Date of Formation	Length of Flap, Cm.	Width of Flap, Cm.	Time, Days	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	26	M	3/31/30	11.0	5.5	10	5.5	5.0	2.0	1.5
2	29	F	4/13/27	17.0	8.0	10	4.2	3.5	4.0	3.2
3	34	M	1/ 9/28	13.5	6.2	8	4.0	3.5	5.0	4.5
4	55	M	7/14/30	11.0	6.0	26 15	No change 3.5	3.0	2.6	2.0

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

The innervation was cut in raising all these flaps. The lower ends of all, except the flaps in case 1, were in areas supplied by the trigeminal nerves of the other side. This accounts for the nearly complete absence of sensations in these flaps. On account of the necessity of transfer within two weeks none were preserved long enough to determine what the rate of regeneration would be.

The double-pedicle flaps raised on the abdominal wall were all used as gauntlet flaps and transferred immediately on the hand. The innervation of this area is from the anterior terminal branches and the lateral branches of the ninth, tenth, eleventh and twelfth thoracic nerves. All these are mixed sensory and motor nerves.

These flaps were raised with the upper ends near the midline of the abdominal wall toward the costal margins and the lower ends toward

the flank almost at right angles to the courses of the nerves. The width, however, prevented the complete loss of sensations. There was no regeneration after twenty-six days.

These areas are innervated by the eleventh and twelfth thoracic nerves, the lateral cutaneous nerve of the thigh, the genitofemoral nerve,

TABLE 4.—*Double-Pedicle Flaps Raised from the Thigh, Calf and Leg*

Case	Age	Sex	Date of Formation	Length of Flap, Cm.	Width of Flap, Cm.	Time, Days	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
Thigh										
1	28	M	1/ 5/27	23.0	12.0	10	11.0	6.5	1.0	0.0
2	50	M	12/ 5/32	7.0	5.0	10	2.6	2.0	1.9	1.3
Calf of leg										
3	21	M	11/ 8/29	12.6	5.5	10	3.7	3.2	1.4	1.0
4	24	M	1/ 8/29	10.5	5.2	12	3.5	2.7	1.8	1.2
5	21	M	12/30/29	13.0	6.0	11	4.1	3.5	1.5	1.1

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

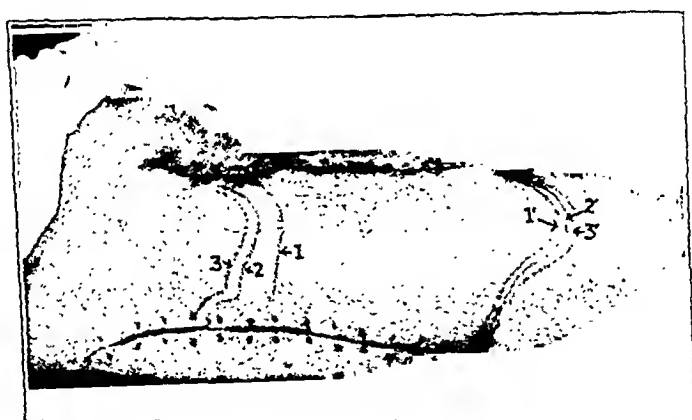


Fig. 3 (case 1, table 4).—Delayed transfer flap with a double pedicle raised from the thigh. A shaped piece of rubber dam had been placed between the flap and thigh. The curves marked on the flap indicate the limits of the sensations. The lines 1 and 1' show the limit of prick sensation. The lines 2 and 2' show the limit of temperature sensation. The lines 3 and 3' show the limit of light touch sensation. Note that at the lower end of the flap toward the knee the sensations are absent beyond the limit of the flap. The readings were taken on the tenth day after raising the flap.

the intermediate and medial rami of the femoral nerve, the lateral cutaneous nerve of the leg, the saphenous nerve and the superficial peroneal nerve. The lateral cutaneous nerve of the thigh is a sensory nerve, and all the others are mixed sensory and motor nerves.

"Upper end" refers to the end of the flap highest up on the extremity. All these flaps were formed in a direction parallel to the course of the nerves. The upper ends therefore have much more innervation than the lower.



Summary: All the double-pedicled flaps with the exception of those raised on the thigh and leg were formed across the courses of the nerves. The flaps on the forehead were narrow and had very little sensation. Those on the abdominal wall were half as broad as long and had sensations in both pedicles even though they had been raised across the courses of the nerves. The upper ends of the flaps raised on the thigh had more sensation than the lower ends because they were formed in a direction parallel to the course of the nerves.

*Tubed Flaps.*—Tubed flaps are double-pedicled flaps in which the edges are sutured margin to margin, thus making a tube completely covered by skin and enclosing the subcutaneous tissue. The transfer on all tubed flaps is necessarily delayed. The data on the tubed flaps are grouped into four tables depending on the anatomic areas in which the flaps were raised.

TABLE 5.—*Tubed Flaps on the Neck*

Case	Age	Sex	Date of Formation	Length of Tube, Cm.	Circumference, Cm.	Time	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	8	M	3/14/27	11.5	4.5	13 days	2.5	2.2	2.4	2.0
2	48	M	12/16/29	11.0	4.3	12 days	2.4	1.5	2.0	1.6
3	6	F	1/18/29	10.7	4.0	10 days	2.3	1.8	2.0	1.3
4	16	F	4/ 2/28	10.3	4.6	4 days	2.0	1.0	1.0	0.5
					4.4	1 mo.	2.7	2.2	1.8	1.0
					4.3	7 mos.	Sensations all present			

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

The flaps were often formed with the upper pedicle behind the ear at about the level of the hair-line and ran from this point diagonally across the neck with the lower pedicle above or below the clavicle. These flaps were usually raised in the area innervated by the anterior branches of the second, third and fourth cervical nerves, which help to form the cervical plexus and emerge as the following cutaneous nerves: the lesser occipital, the great auricular, the cutaneous nerve of the neck and the supraclavicular nerves. These are all pure sensory nerves.

“Upper end” refers to the end of the tube on the head and “lower end,” to the end on the neck or chest. The sensation of temperature was felt between the lines of prick and touch.

These tubes were raised across the courses of the cutaneous nerves destroying the innervation along the shafts and leaving only a short portion with sensations at each end. More than half of the length of every tube was without sensations.

Inasmuch as these four tubes are all approximately the same length and circumference, we can consider the regeneration as one complete picture. Apparently there was no regeneration of sensations in from

four to ten days. The slight edema present after the formation of the tube could account for the difference in the readings at four and at ten days by causing a dulness which would obscure the definite limit of sensation. In one month there was a definite advance in the returning sensations, and they had completely returned in seven months. The sensations must have been carried in by the great auricular nerve above and the middle and anterior supraclavicular nerves below, since the pedicles were in the regions innervated by these nerves.

The flaps raised on the arm were made on the inner side with the upper pedicle near the axilla and the lower toward the elbow. This area is innervated by the axillary nerve, the posterior cutaneous nerve of the arm, the medial cutaneous nerve of the arm and forearm and

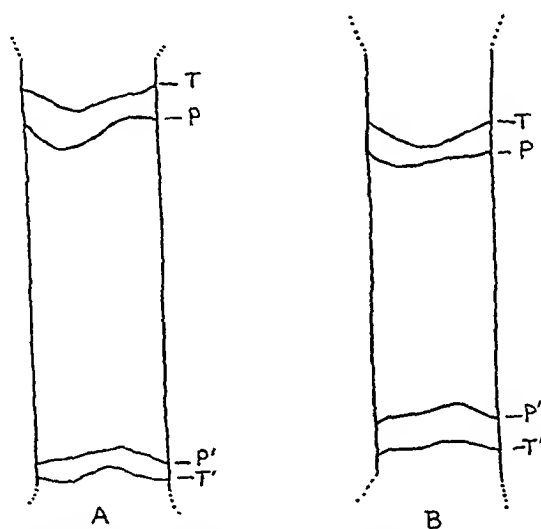


Fig. 4 (case 4, table 5).—Tracings of sensation tests on a tubed flap raised from the neck (one-half actual size). *P* and *T* indicate the lines of prick and light touch sensation on the upper end of the tube. *P'* and *T'* indicate the lines of prick and touch on the lower end of the tube. *A* shows the tracing made four days after the tube was formed; *B*, the tracing on the same tube made one month after the tube was raised. Note that the sensations do not advance in even, regular lines. The readings taken for the tables are the points of greatest advance measured from the base of the tube. The sensations advance from both ends, finally meeting somewhere on the shaft. There has been an appreciable gain in sensations during one month as can be noted by comparing *A* and *B*. The tracings were made on transparent material which was wrapped around the tubed flap and then spread out and redrawn.

the intercostobrachial nerve. The axillary and the posterior cutaneous nerves are mixed nerves while the others are pure sensory nerves.

"Upper end" refers to the end of the tube toward the axilla and "lower end," to the end of the tube toward the elbow. The sensation of temperature was felt between the lines of touch and prick.

These tubes were raised in a direction about parallel to the course of the nerves so that the innervation of the skin used in the tubes was not as greatly interfered with as in the first series of tubed flaps

TABLE 6.—*Tubed Flaps Raised on the Arm*

Case	Age	Sex	Date of Formation	Length of Tube, Cm.	Circumference, Cm.	Time	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	25	M	1/22/30	10.0	4.0	10 days	5.1	4.5	2.7	2.3
2	35	F	10/ 9/29	10.2	4.3	7 days	5.0	4.4	2.5	2.0
3	32	F	6/21/29	10.4	4.0	6 days	5.4	4.7	2.6	2.2
4	31	F	2/10/32	10.0	4.3	10 days	4.8	4.2	3.0	2.4
5	21	M	2/13/33	12.2	5.1	2 days	6.1	5.0	3.1	2.5
					5.0	11 days	6.3	5.2	3.2	2.7
					4.8	1 mo.	6.8	5.5	3.5	3.0

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

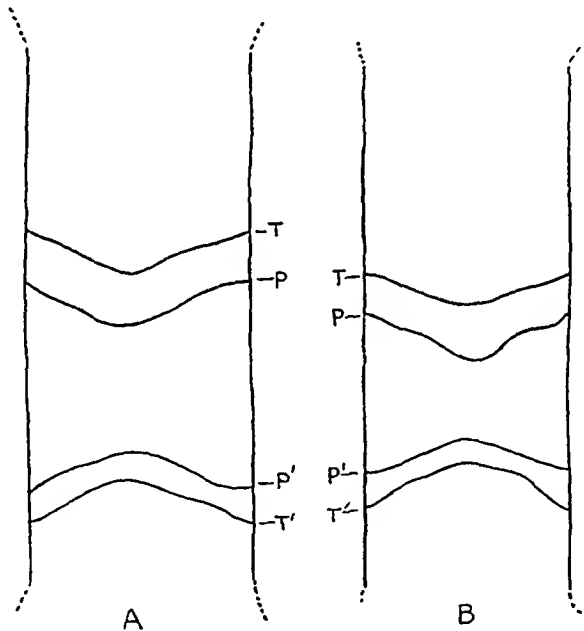


Fig. 5 (case 5, table 6).—Tracings of tests on a tubed flap raised from the arm (one-half actual size). *P* and *T* are the limits of prick and light touch on the upper end of the tube, and *P'* and *T'* are the limits of these sensations on the lower end of the tube. *A* shows the curves after two days; *B*, the curves after one month. There has been a fairly marked gain in sensations on the upper end of the flap after one month, while on the lower end the gain has been much less marked. The sensations of heat and cold are found between the curves of prick and light touch. Note that the sensations in this flap are farther down the shaft of the tube than in figure 4 because the flap was cut in the direction of the course of the innervating nerves, while the flap in figure 4 was cut across the nerves.

(table 5). The innervation of this series is therefore more completely present on the tubed flaps, as can be seen from the table. The difference in the readings in case 5 for two days and eleven days can be

accounted for by the disappearance of the edema which may have partly numbed the tube.<sup>9</sup> There was apparently some regeneration of sensations after one month.

TABLE 7.—*Tubed Flaps Raised on the Abdominal Wall*

Case	Age	Sex	Date of Formation	Length of Tube, Cm.	Circumference, Cm.	Time	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	12	F	3/25/27	14.0	4.5	10 days	4.2	3.7	2.7	2.3
2	12	M	6/18/26	13.0	5.0	9 days	3.8	3.2	3.0	2.5
3	26	M	5/11/28	14.2	5.0	10 days	3.0	2.5	2.6	2.1
4	16	M	1/12/28	12.5	5.1	12 days	3.2	2.5	2.0	1.5
5	17	M	3/13/31	10.5	5.5	10 days	2.8	2.4	1.8	1.2
6	42	M	4/ 6/32	12.0	5.2	3 mos.	3.7	3.3	3.0	2.4
					6.0	6 days	3.5	2.3	1.5	1.0
					5.5	7 mos.	5.3	4.7	3.0	2.7

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

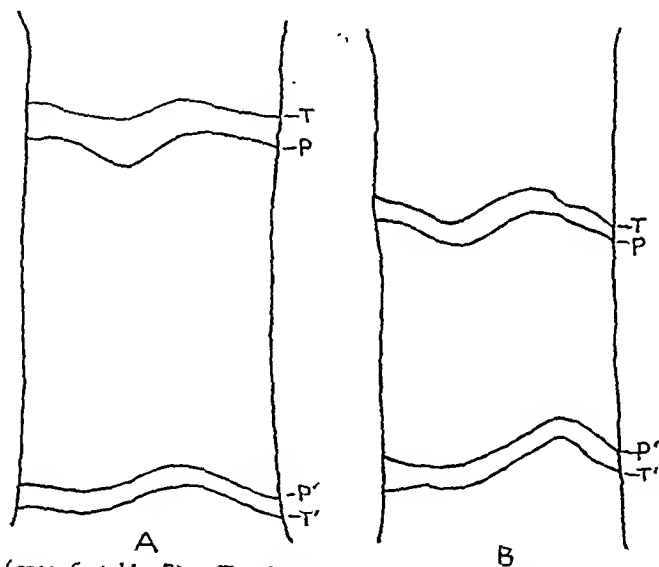


Fig. 6 (case 6, table 7).—Tracings of tests on a tubed flap raised from the abdominal wall (one-half actual size). *P* and *T* indicate the limits of the sensations of prick and light touch at the upper end of the tube near the costal margin and *P'* and *T'* indicate the limits of these sensations at the lower end of the tube on the abdominal wall. *A* is a tracing made six days after the formation of the tube. *B* is a tracing made seven months after the formation of the tube. Note the uneven line of advance of the sensations. The sensations were coming in faster from the upper end which is parallel to the normal course of the nerves in this area.

The tubed flaps raised on the abdominal wall extend from the margin of the ribs in the midaxillary line diagonally across the abdomen on the same side toward the pubis for varying distances but never

9. Postoperative transient paralyses and those caused by the use of crutches may possibly be explained on the same basis.

beyond the midline. This area is innervated by the anterior terminal branches and the lateral branches of the ninth, tenth, eleventh and twelfth thoracic nerves. All of these nerves are mixed nerves.

"Upper end" refers to the end of the tube near the costal margin and "lower end," to the end toward the pubis. The temperature sensations were felt between the lines of light touch and prick.

These tubes were raised across the courses of the nerves so that the innervation to the greater part of the tubes was destroyed. About one half of the tube did not have sensation. The sensations regenerate from both ends gradually toward the center of the shaft of the tube. The upper end retains its sensations for a longer distance than the lower end because this end is more in line with the course of the nerves. In case 5 the sensations came back in about two thirds of the tube in three months, and in case 6 they regenerated in about three fourths of the tube in seven months. It would probably take about one year for the sensations to return completely.

TABLE 8.—*Tubed Flaps Raised on the Back*

Case	Age	Sex	Date of Formation	Length of Tube, Cm.	Circumference, Cm.	Time	Upper End*		Lower End*	
							Prick	Touch	Prick	Touch
1	28	F	5/10/27	42.0	5.2	3 wks.	3.5	3.0	4.3	3.5
2	43	F	5/ 3/27	33.5	6.0	3 mos.	6.5	4.5	7.0	6.0
3	46	M	3/ 2/26	18.0	5.0	17 mos.	Sensations all present			

\* The figures indicate in centimeters the distances from the pedicle at which sensations were present on the flap.

The tubed flaps raised on the back were elevated at the level of the shoulder and extended down for varying lengths usually to the level of the sixth rib. This area is innervated by the posterior branches of the fourth, fifth and sixth cervical nerves and the posterior rami of the thoracic nerves. These nerves are all mixed nerves.

"Upper end" refers to the end of the tube near the shoulder and "lower end" to the end down the back. The temperature sensations were found to be present between the lines of prick and touch sensation. In cases 1 and 2 the tubes were of considerable length and were formed with islands of tissue about half way down by de River's method, thus forming really two tubes. Sensations were absent in these islands of skin.

These tubes were formed across the courses of the nerves so that most of the innervation was destroyed. Sensations were therefore present only a short distance on the tubes. In case 3 the tube was shorter and the sensations were all present in seventeen months.

Summary: All the tubed flaps are of about the same length and diameter, with the exception of those raised on the back. Healing was by first intention without infection.

Two factors influence the regeneration of sensations: the relation of the direction of the tubed flaps to the course of innervating nerves, and the type of innervation. All the tubes with the exception of those raised on the arm and the upper ends of those raised on the abdominal wall were formed across the courses of the innervating nerves. The tubed flaps with the exception of those raised on the neck were in areas innervated by mixed nerves. The area on the neck where the flaps

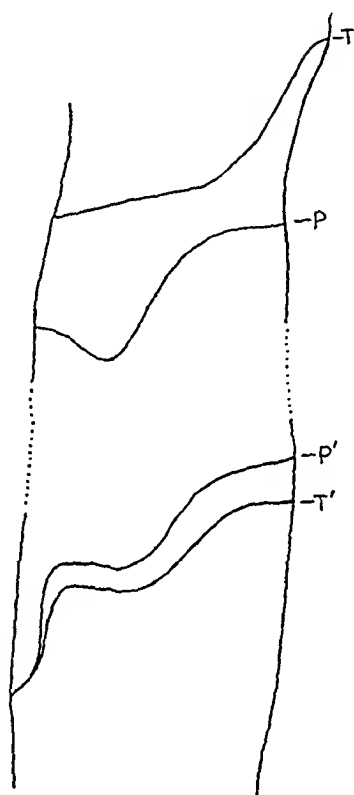


Fig. 7 (case 2, table 8).—Tracings of tests on a tubed flap raised from the back, after three months (one-half actual size). *P* and *T* indicate the limits of prick and light touch on the upper end of the tube raised on the back. *P'* and *T'* indicate the limits of these sensations on the lower end of the tube. The broken line represents the length of the shaft which is not shown in the drawing. This tube was 35.5 cm. in length.

were raised is innervated by pure sensory nerves. The tubes on the arm were not formed in the areas of the sensory nerves.

When the tubed flaps were formed across the paths of the nerves most of the innervation was destroyed regardless of the type of innervation. The tubes on the arm (table 6), which were raised in the direction of the nerves, had sensations for much longer distances than any of the others. The upper ends of the tubes raised on the abdominal

wall (table 7) had sensations for longer distances in proportion to the sensations of their lower ends than any of the other sets of tubed flaps.

The regeneration of sensations was much more rapid in the tubes raised in the areas of pure sensory nerves than in the areas innervated by mixed nerves. In case 4, table 5, a tube 10.3 cm. long had recovered its sensations in seven months, whereas a tube 12 cm. long on the abdominal wall (case 6, table 7) had recovered sensations for about three fourths of its length in the same time. A tube 18 cm. long on the back (case 3, table 8) had recovered sensation in seventeen months, a much slower rate of recovery than that for the tube on the neck (case 4, table 5), which was 10.3 cm. long.

The measurements of the circumferences of the flaps show that there is a slight shrinkage in the tubes due to the contracting scar; this is not great enough to contraindicate the preservation of tubes over long periods of time.

#### COMMENT

The loss of epicritic touch always exceeded the loss of pain in all the pedunculated flaps tested, and the regeneration of the sensation of pain was always first in all the flaps in which regeneration had taken place.

A review of the anatomy of the superficial nerves will facilitate the explanation of this phenomenon.<sup>7</sup>

The general sensations represented at the periphery are carried by cutaneous nerves which are processes of bipolar cells located in the posterior root spinal ganglions. According to the most widely used theory there are two distinct superficial systems: the protopathic and the epicritic. The protopathic system is the more primitive, and through it the grosser forms of sensation are conveyed. It gives information of pain and of extreme degrees of heat and cold and is not sharply localized. The epicritic system carries information of finer tactile impressions and mild degrees of heat and cold and is finely graded and definitely localized.

All these fibers enter the spinal cord through the posterior nerve roots, and a regrouping immediately takes place. All sensations of a similar nature, whether protopathic, epicritic or deep, are grouped together, with the exception of a few tactile fibers. There are only four groups in the spinal cord: thermal, pain, tactile and muscle sensations. The fibers carrying thermal, pain and tactile sensations end around cells at the tip of the posterior horn of the cord, and a new set of fibers from these cross to the opposite side of the cord to form the spinothalamic tracts. A few of the fibers of epicritic touch remain

on the same side of the cord with the fibers carrying muscle sensations continuing up in the columns of Goll and Burdach which end in the medulla oblongata, in the gracile and cuneate nuclei. New fibers from these form the mesial fillet which is joined farther on by the spinothalamic tracts. In the pons and midbrain the mesial fillet is divided into two parts: mesial and lateral. The mesial part contains the fibers conveying muscle sensations, and the lateral part carries the thermal, pain and tactile sensations. The mesial fillet ends in the thalamus, and new fibers carry the sensory impulses partly to the essential organ in the thalamus but mainly to the cerebral cortex. The thalamus has the power to recognize certain sensations in a crude manner but is unable to localize them. The finer analysis of sensations is made in the cerebral cortex.

If the spinal cord is injured general sensations will be lost to all parts the nerves of which enter the cord below the point of injury. The demarcation will be the same for all sensations whether they are epicritic or protopathic because the sensations have already been regrouped according to kind. If a nerve is injured before it reaches the cord, the loss of sensations will be in proportion to the extent to which they are carried by the nerves involved. The unit of protopathic supply lies in the posterior roots. No one nerve forms more than a tributary supply of an area innervated by a plexus of nerves, and whenever a single peripheral nerve is destroyed the loss is not complete. Other branches of the same plexus carry pain fibers to the same area by a slightly different route, and these may not have been injured by the trauma. If the injury is extensive enough the area may lose all of its sensations, but the loss will not be as extensive as it would be if only one nerve carried all the sensations to that area. This also explains the more rapid regeneration of the protopathic sensations. Since the sensation of touch as elicited by light pressure is a protopathic sensation, many observers have been led to believe that light touch returns before or with pain instead of after it.

The peripheral nerves form the units of epicritic supply. Each peripheral nerve carries the epicritic sensations from its own area, and the other nerves of the same plexus do not report from the same general area but from specific parts of that area. The loss of epicritic touch sensation is therefore more marked than that of prick or pain. Protopathic temperature sensations are reported in the same manner as pain. However, there are fewer nerve endings for temperature sensations in the skin so that the limits are hard to locate, especially since the manner of testing involved some slight pressure when the skin was touched with the test tubes.



Cutting of the nerves causes a wallerian degeneration<sup>10</sup> of the peripheral stump and some degeneration of the proximal ends. The peripheral stump degenerates rapidly, but all of its constituent parts do not disappear. The parts such as the axon and the myelin which trophically depend on the nerve cell are destroyed, but the parts which do not depend on the influence of the neuron undergo changes which leave them ready to receive and guide the new axons when they begin to grow out. There are tubes empty of axons waiting for the regenerating axons to return to the end-organs. The new axons come in all directions in great disorder seeking the empty tubes and trying to connect with the end-organs. The end-organs apparently have some attraction for the axons so that the axons of epicritic touch seek the end-organs of the same sensation and so on.

In the pedunculated tubed flaps formed across the nerve courses the empty nerve tubes were at right angles to the course of the regenerating nerves. The regenerating nerve axons therefore had to come to the ends of the empty tubes and then go across to the nerve endings or make new channels directly to the end-organs. Either course would cause the regeneration to be much slower than if the direction of the empty tubes and that of the regenerating axons were the same. This was demonstrated in our cases. The tubed flaps raised on the neck and abdominal wall were formed across the course of the nerves while the tubed flaps raised on the arm were parallel to the course of the nerves. The regeneration of the sensations was much faster in the flaps on the arm than in either of the other two groups.

Another factor enters into the rate of regeneration. Some of the peripheral nerves conveying general sensations come from nerves which are purely sensory while others come from nerves which also give motor fibers to muscles before ending in the sensory peripheral branches. These so-called motor nerves are apparently composed of both sensory and motor nerve fibers which separate at the cord. The rate of regeneration in these mixed nerves is slower than the rate in those which are parts of purely sensory nerves. The axons must experience greater difficulties in regenerating from the complex nerve stumps. We found that the rate of regeneration was much slower in the flaps raised in the areas innervated by the mixed nerves.

It is apparent from these tests that there is no evidence of regeneration of the sensations until after the third week. A double-pedicle flap raised on the abdominal wall (case 3, table 3) showed no change in reactions to the tests twenty-six days after its formation. Tubed flaps showed an increase in sensations one month after formation. None of

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10. Ramón y Cajal, S.: *Degeneration and Regeneration of the Nervous System*, translated by R. M. May, New York, Oxford University Press, 1928, vol. 1.

the patients could be followed after their discharge from the hospital, so that the rate of regeneration cannot be calculated. In analyzing the flaps in which sensations have partly or completely returned, we can roughly estimate the rate of regeneration at about 1 cm. per month.<sup>11</sup> This naturally varies with the location, width and length of the flaps because all these factors aid or retard the growth of the axons. A tubed flap 10.3 cm. long and 4.6 cm. in circumference raised on the neck (case 4, table 5) showed a return of sensations of 1 cm. per month. A tubed flap 10.5 cm. long and 5.5 cm. in circumference raised on the abdominal wall (case 5, table 7) showed a return of sensations of 0.7 cm. per month, and a second tube (case 6, table 7) 12 cm. long and 6 cm. in circumference also raised on the abdominal wall showed a rate of regeneration of 0.5 cm. per month. Neither of these tubes had completely received their sensations at the time of the test, and it is problematic whether the rate would have changed later on if the tubed flaps had been kept intact. A tubed flap raised on the back (case 3, table 8) had recovered all sensation after seventeen months. We do not know, however, when this return had been completed.

The clinical value of these observations is important. Inasmuch as the nerve supply in pedunculated flaps has been interfered with more or less seriously the patient is not warned by pain as to injury. Therefore great care must be exercised when handling flaps and applying dressings to avoid injury, because the normal sensations which would convey this information of danger are absent. Compresses which are too hot or dressings which are so tight as to interfere with circulation will not be noted by the patient. Tissues in which protopathic sensations are lost apparently do not heal as readily as normal tissue. We have noted that tubed flaps transplanted after the sensations have completely returned appear to heal better than those transplanted before this regeneration has returned, but the fact that the blood supply in these flaps is also completely adequate must also be borne in mind.<sup>12</sup>

Apparently age has no influence on the amount of degeneration or on the rate of regeneration of superficial sensations. In our series, composed of patients ranging from 6 to 60 years, no definite difference was found.

#### SUMMARY

There are two superficial systems of peripheral sensations depending on two sets of nerves. The extent of loss of sensations depends on

11. The rate of regeneration as observed by us is considerably slower than that noted in the textbooks in which the rate is usually given as about 1 mm. per day when nerves have been divided and sutured.

12. German, W.; Finesilver, E. M., and Davis, J. S.: The Establishment of Circulation in Tubed Skin Flaps. An Experimental Study, *Arch. Surg.* 26:27 (Jan.) 1933.

the extent to which nerve destruction occurs. The degree of the loss depends to a certain extent on the direction of the pedunculated flap in regard to the direction of the innervating nerves. In pedunculated flaps the loss of pain is always greater than the loss of epicritic touch.

Temperature sensations were usually found between the lines of prick and touch. The nerve supply in newly formed pedunculated flaps is usually interfered with to such a degree that every care must be taken to protect the flap from injury. The regeneration of sensation appears to be faster in flaps raised in areas innervated by pure sensory nerves than in areas innervated by mixed nerves.

# GASTRIC ACIDITY AS INFLUENCED BY PYLORIC CLOSURE AND STENOSIS

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It has become increasingly evident that the acidity of gastric contents depends not entirely on variations in the secretory activity of the stomach, but also on the degree to which the secreted acid is neutralized. It has been demonstrated, for example, that pure gastric juice, actively secreted, reaches a constant acidity of about 0.5 per cent hydrochloric acid (about 140 degrees). As found in normal gastric contents after an adequate stimulus, the acidity is much lower, indicating that this value has been reduced until it is usually about from one third to one fourth of this level. Although it is generally agreed that neutralization brings about this reduction, there is still some dispute about its mechanism.

From a variety of evidence summarized in previous communications from this clinic,<sup>1</sup> it appeared that this neutralizing action took place in the stomach largely by the action of regurgitated alkaline pancreatic juice, which combined with the hydrochloric acid and thus kept gastric acidity within limits usually designated as normal. If this theory holds true, it is obvious that whatever initiates regurgitation, the pyloric sphincter must play a decisive rôle by controlling the degree to which reflux can occur. We accordingly investigated the relation between the activity of the sphincter and the neutralization of gastric acidity. In our first experiments,<sup>1c</sup> we produced an insufficiency of the sphincter by performing a careful pyloromyotomy, after which we noted a marked and persistent lowering of gastric acidity, shown by a more rapid and complete neutralization of an acid test solution. The present paper is concerned with a series of observations already mentioned in a brief preliminary note,<sup>2</sup> in which the converse experiment was performed;

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From the department of surgery, Washington University School of Medicine, and Barnes Hospital.

1. (a) Elman, R.: Probable Influence of Pancreatic Juice in Regulation of Gastric Acidity, *Arch. Surg.* **16**:1256 (June) 1928; (b) *Surg., Gynec. & Obst.* **49**:34, 1929. (c) Elman, R., and Rowlette, A. P.: Rôle of Pyloric Sphincter in Behavior of Gastric Acidity, *Arch. Surg.* **22**:426 (March) 1931.

2. Elman, R., and Eckert, C. T.: *Proc. Soc. Exper. Biol. & Med.* **30**:1343, 1933.

i. e., partial or complete pyloric closure was produced, and its influence on the behavior of gastric acidity was then studied.

#### PREVIOUS OBSERVATIONS

A number of investigators produced partial pyloric stenosis experimentally. Bolton,<sup>3</sup> in 1909, did so by encircling the pylorus of twenty-nine cats with a rubber tube of appropriate size. Although he did not especially study the acidity of the contents of the stomach, he observed that experimental gastric ulcers in the cats which survived showed definite evidence of delayed healing, sclerosis and incomplete regeneration, as compared with the rapid healing in cats without pyloric stenosis. Tumpeer and Bernstein<sup>4</sup> injected liquid petrolatum under the pyloric muscle of six dogs, but were unable to produce a stenosis. Although the dogs were observed for seven months, there was no change in the gastric emptying time, and no dilatation of the stomach was found at autopsy. No measurements of acidity were reported.

Of more direct application to the present study are the experiments of Hamburger and Friedman,<sup>5</sup> who tied a silk ligature about the pylorus of dogs and studied the acidity of the gastric contents before and after operation. In ten dogs, a complete stenosis was produced; as might have been expected, a fatal outcome developed within a few days, undoubtedly from dehydration and alkalosis due to vomiting. In ten other dogs, a silk ligature was tied loosely. The result was a moderate stenosis which brought about slight or no changes in acidity, but which may be considered as a control observation for the third series of nine dogs in which a marked stenosis was effected. These animals had symptoms, lost weight and died in from three weeks to two months. The acid values after a test meal were much higher than before operation, and the contents of the fasting stomach showed acidities as high as 90 degrees, whereas acid was rarely found in normal controls. Of considerable interest, too, is the fact that two of these animals were described as dying of general peritonitis from perforation of a spontaneous duodenal ulcer located just beyond the site of the occluded pylorus.

Ivy, Droegemueller and Meyer<sup>6</sup> studied gastric acidity as influenced by pyloric stenosis, which was produced by means of a tape or a metallic band. The dogs were also provided with Pavlov pouches, and the acidity of the pure gastric juice obtained from them was studied. The

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3. Bolton, C.: *Proc. Roy. Soc., London*, s.B **82**:233, 1909.

4. Tumpeer, I. H., and Bernstein, M. A.: *Experimental Pyloric Stenosis*, *Am. J. Dis. Child.* **24**:306 (Oct.) 1922.

5. Hamburger, W. W., and Friedman, J. C.: *Contributions to the Experimental Pathology of the Stomach*, *Arch. Int. Med.* **14**:722 (Nov.) 1914.

6. Ivy, A. C.; Droegemueller, E. H., and Meyer, J. L.: *Effect of Experimental Pyloric Stenosis on Gastric Secretion*, *Arch. Int. Med.* **40**:434 (Oct.) 1927.

results, in general, were somewhat equivocal. However, in two of the seven dogs, the acidity of the contents of the main stomach was measured. In these animals the acid value after a test meal reached a high point of 158 and 130 degrees, respectively, which is far greater than occurs normally; it is equal, in fact, to the high acidity of pure, actively secreted juice. Of additional interest is the fact that in one of the dogs a perforating duodenal ulcer was found at autopsy. Similar experiments were described by Zukschwerdt,<sup>7</sup> who produced pyloric stenosis by a strip of fascia in dogs previously provided with a pavlov pouch and showing a standard secretion response. The secretion of the pouch after stenosis was produced was more prolonged and 50 per cent greater in amount. The high acidity of the pure juice secreted by the pouch remained the same, from 0.4 to 0.5 hydrochloric acid, which is the maximum acidity ever developed by the gastric juice. Unfortunately, no studies of the acidity of the contents of the main stomach were made. The prolonged emptying time, shown by roentgenogram after a meal of barium sulphate, demonstrated that a marked pyloric stenosis had been produced. Adequate control experiments were also described. At autopsy, the mucosa of the main stomach showed marked hyperemia and erosions in the lesser curvature; the mucosa of the pouch was normal. Webster and Armour<sup>8</sup> described dogs with pyloric obstruction kept alive through jejunal feedings. They secreted through a gastric fistula a juice of high acidity (from 0.4 to 0.5 per cent hydrochloric acid). In two of the dogs, ulcers were observed at the site of the fistula. Hoelzel and Da Costa<sup>9</sup> noted that in some rats on a restricted protein diet pylorospasm developed, indicated by gastric retention, and at the same time there was definite evidence of increased gastric acidity. Boldyreff,<sup>10</sup> in more or less acute experiments, showed a failure of neutralization of an acid solution after the pylorus was served.

Turning to observations on man, one finds that while instances of pyloric stenosis are frequently described, the data on gastric acidity are equivocal. In many cases, the stenosis, due to cicatricial contraction of a duodenal ulcer, was of such long duration that gastric dilatation and stasis had undoubtedly affected the secretory power of the mucosa. Delayed or absent neutralization of an acid test solution was found in several of such cases by one of us (Dr. Elman).<sup>11</sup> In other cases described as hypertrophic pyloric stenosis in adults, definite hyperacidity was described.<sup>11</sup>

7. Zukschwerdt, L.: *Ztschr. f. d. ges. exper. Med.* **79**:578, 1931.

8. Webster, D. R., and Armour, J. C.: *Canad. M. A. J.* **27**:240, 1932.

9. Hoelzel, F., and Da Costa, E.: *Proc. Soc. Exper. Biol. & Med.* **29**:979, 1929.

10. Boldyreff, W.: *Ergebn. d. Physiol.* **11**:121, 1911.

11. Bastianelli, R.: *Pyloric Spasm and Its Surgical Treatment*, *Ann Surg.* **81**:45 (Jan.) 1925.

A frequent type of hypertrophic stenosis of the pylorus occurs in infants, and one may find occasional references to the high acidity of the gastric contents of these patients. The most complete study, however, was made recently by M. J. E. Senn at the St. Louis Children's Hospital. Senn examined the gastric contents of a great many infants, and among normal controls he found, as did Marriott and Davidson<sup>12</sup> a few years ago, an average  $p_H$  of 3.75, with an extreme range from 2 to 5.<sup>13</sup> In children with hypertrophic pyloric stenosis (proved by operation), the acidity was much higher; the fasting contents showed an extreme range between  $p_H$  1.8 and  $p_H$  3. Moreover, no reduction of this acidity was found after a test meal of diluted cow's milk which, in normal babies, exerts a definite neutralizing action, owing to its buffer content. After operation (pyloromyotomy), a decided change was observed, the  $p_H$  showing a pronounced alkaline shift, i. e., values of 4.5 and sometimes as high as 7. This change, following relief of the pyloric barrier, could hardly be due to anything but a reflux of alkaline duodenal contents. As further evidence that this is probably the explanation, Senn noted that the gastric contents, sterile before operation, after division of the hypertrophic sphincter, often contained *Bacillus coli*, which could obviously have originated only by reverse peristalsis carrying intestinal contents into the stomach.<sup>14</sup>

#### METHODS

As in our previous studies, the behavior of gastric acidity was studied by means of an "acid test meal." Two hundred cubic centimeters of 0.5 per cent hydrochloric acid was introduced by a small stomach tube, and 20 cc. samples were aspirated immediately and every twenty minutes thereafter until the stomach was empty or until it was obvious that gastric emptying was delayed, in which case the retained contents were removed and measured. Samples were titrated with tenth-normal sodium hydroxide, using phenolphthalein as an indicator. A fast of twenty-four hours preceded each neutralization test. In one dog, secretion curves were obtained by using histamine as a stimulant.

Healthy adult dogs of medium size (from 6 to 10 Kg.) were used. Operations were carried out under ether anesthesia with aseptic precautions. If vomiting occurred after operation, the animal was either treated parenterally with saline solutions for several days or killed immediately with chloroform. Only animals without symptoms and in good general condition were used for postoperative observations.

In a first series of experiments, attempts were made to produce pylorospasm by encircling the pylorus with rubber elastic and, later, silver coil springs. This did not succeed, for one reason or another, so in all subsequent experiments a

12. Marriott, W. M., and Davidson, L. T.: Acidity of Gastric Contents of Infants, *Am. J. Dis. Child.* **26**:542 (Dec.) 1923.

13. Marriott, W. M.; Hartmann, A. F., and Senn, M. J. E.: *J. Pediat.* **3**:181, 1933.

14. Senn, M. J. E.: Unpublished observations.

stout silk ligature was passed around the pyloric ring and tied securely; in the tie was included the tip of a hemostat, which on removal left just enough slack to avoid a complete pyloric closure. A bit of omentum was then wrapped over the ligature to prevent adhesions. We found that the effect was apt to be more prolonged if the ligature was first soaked in 25 per cent silver nitrate, which seemed to promote scarring and lessened the tendency for the ligature to become loose. This, nevertheless, did occur not infrequently after a lapse of several weeks or months. It is possible that strips of fascia would have proved more satisfactory. After operation, neutralization tests were carried out occasionally as early as the first day; ordinarily, however, in a week or two, and in a few instances in a month or more. Autopsies were performed in all cases. Some dogs died spontaneously of pneumonia or of other causes not connected with the experiment at various times after operation. The others were killed with chloroform.

In a second series of dogs, at operation we installed a pyloric snare in order to be able to open or close the pylorus at will in the unanesthetized animal. The snare described by Maddock<sup>15</sup> was first tried, and in a few dogs significant observations were made. A ligature is passed around the pylorus, and the ends are carried through a glass tube and brought out through the abdominal wall, one on each side of the incision, the glass tube remaining in the abdomen after the wound is closed. Now, by drawing out on the two ends, traction is exerted around the pylorus, thus closing it against the deep end of the tube. This device generally worked well for a few days but, as might be expected, infection soon set in, whereupon it was necessary to terminate the experiment. We later used a small silver tube, about 2 mm. in diameter, provided with two tiny loops or holes at one end. A gold wire was attached loosely to one of the loops; the other loop was sutured to the anterior wall of the pylorus. The free end of the wire was passed around the sphincter and led through the tube and out of its other end, which was then made to traverse the abdominal wall through a separate tiny puncture wound in the right lumbar region. Omentum was wound around the tube and the incision was closed. The free end of the silver tube holding the free end of the wire was protected by strapping a thin wicker basket over it. Observations were started within a few days and, when possible, continued for several weeks after operation. The usual test solution of 200 cc. of 0.5 per cent hydrochloric acid was given by a stomach tube, and samples were withdrawn every twenty minutes. By drawing the wire out (a stickpin clasp passed over the wire kept it from slipping back), the pylorus was constricted; by pushing it in, it was released. Its effect on the neutralization of the test solution was observed. The greatest difficulty, in any case, was knowing how much tension to exert, particularly after several weeks when a good deal of inflammatory tissue had grown around the apparatus. The eventual scarring, too, often made repeated observations impossible, for in such a case neutralization of the acid solution did not occur even when the snare was kept loose.

#### EXPERIMENTAL FINDINGS

*Permanent Partial Pyloric Stenosis.*—In this group, there were twelve dogs in which a definite delay in the neutralization of the acid test solution was found after pyloric stenosis was produced. Figure 1 represents the findings in six of them, and shows the ineffective

15. Maddock, S. J.: J. Lab. & Clin. Med. 17:369, 1931.



neutralization of the acid solution after pyloric stenosis, as compared with the preoperative controls. The emptying time, shown by gastric residues, was often prolonged. Fasting contents, which normally have no titrable acidity, were examined in some of the dogs with pyloric stenosis. Their acid values were always high, and twice were 140 degrees, which is as strong as gastric contents ever get, representing, therefore, the high acidity of pure, actively secreted gastric juice.

In dog 340, in addition to neutralization curves (fig. 1), curves of gastric secretion were obtained, using 1 mg. of histamine as the stimulant, injected intramuscularly. Figure 2 shows the decided increase

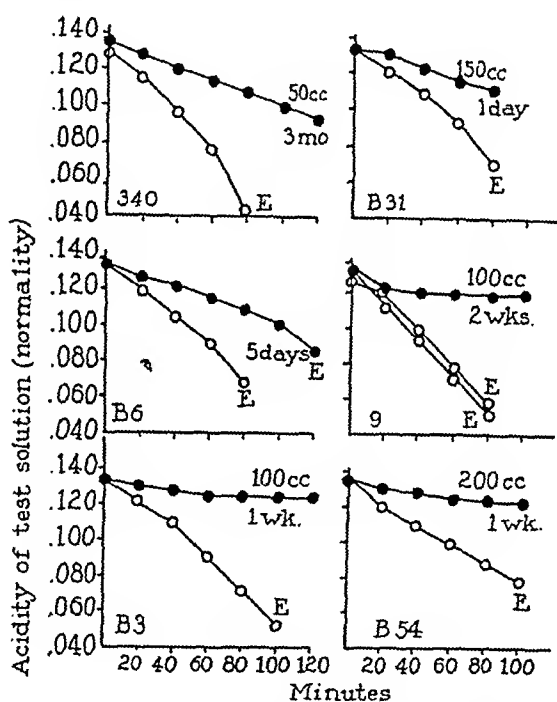


Fig. 1.—This shows the neutralization curves of six dogs before (lower curve) and after (upper curve) pyloric stenosis was produced by a silk ligature at operation. The interval in days, weeks or months is indicated in each case. E indicates the stomach was empty. The figures in cubic centimeters above the upper curves indicate the amount of contents removed at the conclusion of the test. The two lower curves for dog 9 were obtained before and after a loose pyloric ligature was tied; the upper curve, two weeks after a second but tighter ligature was placed.

in amount as well as in acidity of the gastric juice three months after pyloric stenosis had been produced, as compared with the preoperative control.

Control experiments, described in a previous paper,<sup>1c</sup> showed that simple laparotomy does not influence the rate of neutralization; in seven of the twelve dogs in the present group control curves were made before pyloric stenosis was produced. In the five in which these

were not made the postoperative change was the same as in the others. One of the twelve dogs was an inadvertent control; after a pyloric ligature was tied no change was observed, whereon a second operation was done which revealed that the tie was loose. On placing a second, tighter ligature, definite delay in neutralization was found (fig. 1, dog 9). Additional controls were also furnished by a number of the earlier experiments, when no change was noted after operation, and when autopsy showed that the ligature had slipped or had been tied loosely.

The observations at autopsy in the twelve successful experiments proved of additional interest. The stomach in some cases showed scarcely any change in size; in others, it was dilated and in some the

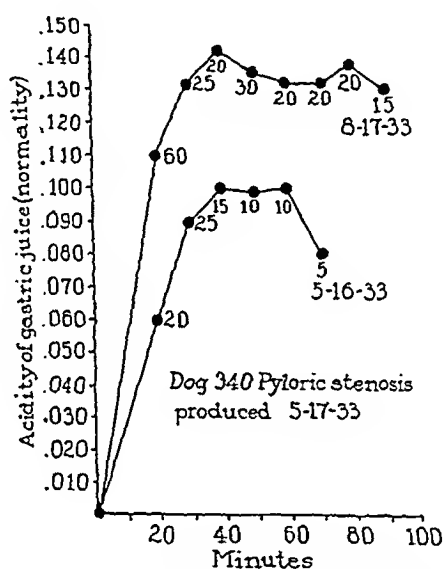


Fig. 2.—Secretion curves (after the injection of 1 mg. of histamine intramuscularly) obtained before and three months after effective pyloric stenosis had been produced. Neutralization curves for this dog are shown in figure 1. The figures refer to the amounts of gastric contents obtained. Note the greater amount (210 cc. as against 85 cc.) as well as the greater acidity with the pylorus partly occluded.

wall was hypertrophied. The site of the ligature was in all cases uninfected and covered only with scar tissue and omentum; the pylorus was free and was not adherent to adjacent structures. Pronounced constriction of the lumen of the pylorus was evident in all cases. In some, it was difficult to see how any food had been able to pass at all. With the exception of one case, in which general peritonitis from a perforated duodenal ulcer was found, the peritoneum was clear. On opening the stomach, however, a marked hyperemia of the mucosa, especially of the lesser, curvature, was evident in every case. On microscopic section, a tremendous number of oxyntic cells were seen.

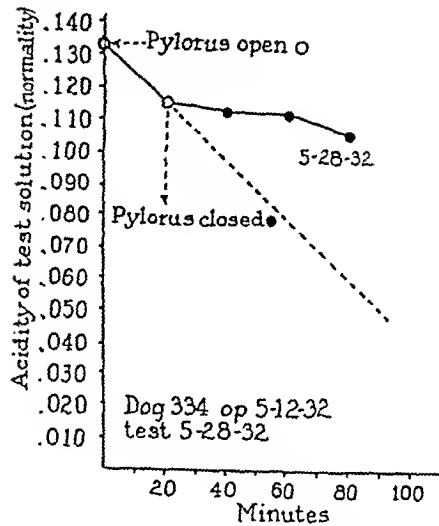


Fig. 3.—Curve obtained with the use of a pyloric snare two weeks after operation. The dotted line is the normal neutralization curve. Note the cessation of neutralization after the pylorus was closed by drawing out on the snare. In this and the following illustrations the open dots indicate titrations while the pylorus was open; the solid dots, titrations when it was closed.

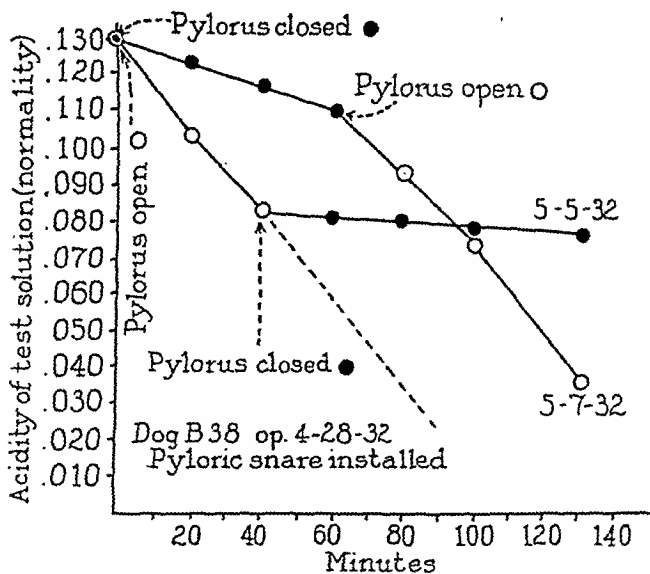


Fig. 4.—Two neutralization curves seven and nine days after operation. The upper curve shows the result when the pylorus was first closed and later opened; the lower curve, the result when it was first left open and then closed. Note the prompt drop in acidity while the pylorus was open and the delay or absence of a drop while the pylorus was closed.

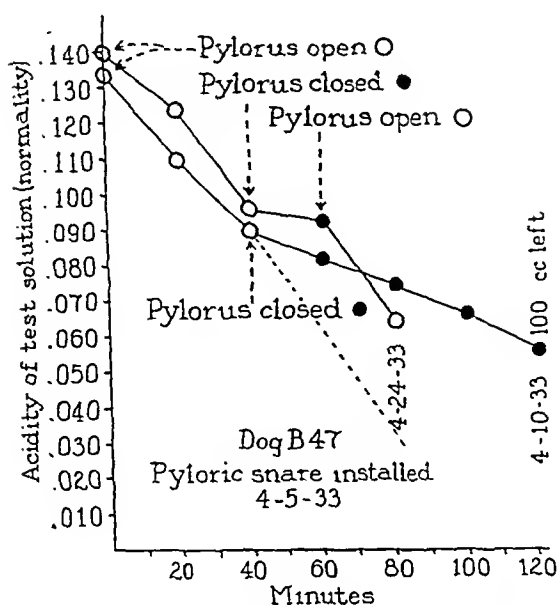


Fig. 5.—Two neutralization curves obtained five and nineteen days after operation. In the lower curve, note the delayed neutralization and emptying (as shown by the residue after eighty minutes) following closure of the pylorus. The upper curve shows three intervals: prompt neutralization with the pylorus open, none with the pylorus closed and a prompt drop of acidity when the pylorus was reopened.

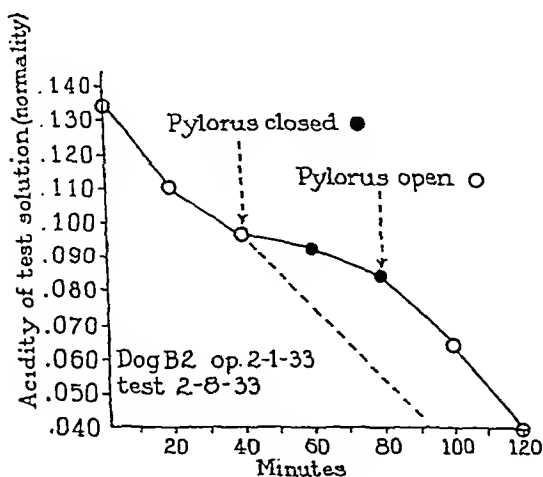


Fig. 6.—Curve for a dog with pyloric snare, seven days after operation. Note the normal drop in acid, its delay as soon as and while the pylorus was closed and its final drop as soon as it was opened again by pushing in on the snare. The broken line indicates the curve of normal neutralization.

Occasionally, small erosions were made out. In the duodenum, marked inflammatory changes were apparent. They were beyond the site of the ligature and consisted of redness, superficial erosions and an out-pouring of exudate. It is planned to describe these changes in greater detail in a subsequent communication.

*Pyloric Snare.*—In this group, ten successful experiments were performed on seven dogs. It was found, briefly, that when the snare was drawn tightly so that the pylorus was presumably closed, little or no neutralization of the acid test solution, previously introduced, took place. However, when the snare was loose and the pylorus was open, neutralization occurred as rapidly as normally. The experiment was

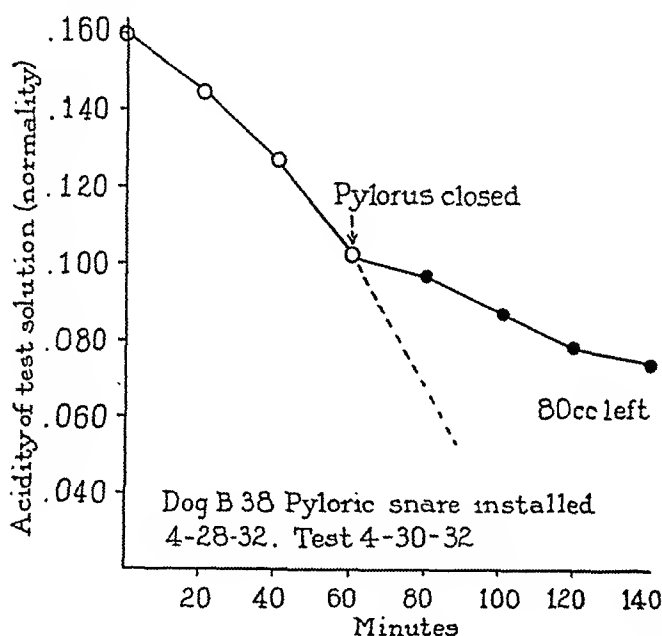


Fig. 7.—Curve obtained with the use of a pyloric snare two days after operation. Note the normal drop in acidity until the pylorus was closed, whereupon neutralization almost ceased, with a retention of 80 cc. after eighty minutes.

varied by either tightening the snare for several twenty minute periods and then loosening it, or first keeping it loose for a time and then tightening it. In two experiments, it was possible to study three intervals: with the pylorus open, then closed and finally open again (figs. 5 and 6). The accompanying graphs represent seven of the ten experiments and are self-explanatory (figs. 3, 4, 5, 6 and 7).

#### COMMENT

A correlation between the level of gastric acidity and the activity of the pyloric sphincter had long been suspected and was made the basis of the well known theory of Cannon, which associated the opening

and closing of the pylorus with the presence of acid in the stomach and duodenum. This theory of the "acid control of the pylorus," based on convincing experimental data, has been more or less universally accepted since it was enunciated in 1907, although Cannon himself pointed out that it failed to explain a good many facts.<sup>16</sup>

The present experiments were designed to study this relationship, but not by observing changes in the pylorus as influenced by gastric acidity, since it is notoriously difficult to know in an intact animal when the sphincter is open or closed. To do so by measuring the emptying time of the stomach is not accurate, for we now know<sup>17</sup> that other factors, such as gastric peristalsis, tone and the rapidity with which the duodenum empties, influence the rate of gastric evacuation as much as or more than the activity of the pylorus. In view of this intrinsic difficulty, it seemed more promising to induce definite change in the pylorus and measure its influence on the level of gastric acidity.

The findings described here are definite and consistent. They show not only that stenosis of the pylorus leads to a high acidity of the fasting contents, but that acid introduced into the stomach cannot be neutralized as completely or rapidly as normally. In some experiments, there was no neutralization after pyloric stenosis was produced. High acidity with pyloric stenosis was noted by other workers both experimentally and clinically, but it was attributed by some<sup>2</sup> to the associated gastric retention which prolonged the secretory phase because of impaired emptying. This can hardly be the explanation of the present findings, for no secretory stimulus was invoked (if we except a slight mechanical effect due to the introduction of the solution used as a test). The delay in neutralization must have been directly connected with the pyloric stenosis. Moreover, in our second series of experiments with the pyloric snare when the stenosis was transient, the same effect was observed; while the pylorus was open, gastric acidity was reduced effectively, and while it was closed, it was reduced slowly or not at all. These findings suggest that the high acidity found by others in cases of pyloric stenosis may also have been due, at least partly, to ineffective neutralization rather than to an increase in the secretory process as a result of the gastric retention.

Of greater significance is the cause of the impaired neutralization resulting from pyloric stenosis or closure. It seems difficult or impossible to explain it on the basis of an intragastric mechanism. How any diluting fluid, suddenly elaborated, or mucus suddenly secreted, could account for the prompt changes noted in our second series of experiments,

16. Cannon, W. B.: *Am. J. Physiol.* 20:283, 1907.

17. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, ed. 2, New York, Paul B. Hoeber, Inc., 1928, p. 178.

when the pylorus was opened and closed at short intervals, is hard to see. In contrast to this supposition, it is easy to understand the findings on the basis that duodenal regurgitation is the mechanism by which the neutralization is largely effected. The pyloric closure, by shutting off the duodenum, prevents reflex mainly of the alkaline pancreatic juice, which has the most efficient power of neutralizing acid in the stomach. Thus, the acid solution which is introduced remains unchanged, and by inference secreted gastric juice likewise (fig. 2, dog 340) remains higher than normal.

The assumption of duodenal regurgitation not only explains the present findings but applies equally well to the observations of Senn,<sup>14</sup> mentioned previously, in a comparable pyloric stenosis which occurs spontaneously in infants, and in which the high acidity of gastric contents gives way to less acid or even neutral contents promptly on release of the pyloric barrier, with many intestinal bacteria in the stomach to add further proof of regurgitation. Additional observations of a converse sort made in this laboratory lend further support to the theory of duodenal regurgitation. In these experiments, more effective neutralization of gastric acidity followed closely on successful division of the pyloric sphincter,<sup>15</sup> which presumably allowed freer access of pancreatic juice into the stomach. Moreover, when pancreatic juice was drained to the outside,<sup>1</sup> neutralization did not occur at all. Matthews and Dragstedt<sup>18</sup> recently showed that neutralization fails when a valve is tied into the pylorus, making duodenal reflux impossible, even when gastric emptying is unobstructed. These observations, too, point to the importance of regurgitation in the control of gastric acidity.

It would seem from all these and other considerations mentioned in previous papers<sup>1</sup> that we may accept the existence of a definite correlation between the pylorus and gastric acidity, but in converse terms of that expressed by Cannon twenty-five years ago. May we not speak of the pyloric control of gastric acidity? If duodenal regurgitation is the important factor in the control of gastric acidity, it is obvious that the pylorus is a decisive link in the physiologic chain.

The anatomic changes in the duodenum, briefly mentioned here, and especially the accidental observation of a perforated ulcer in the same part of the duodenum, i. e., just beyond the exit of the stomach, have a suggestive bearing on the question of the pathogenesis of duodenal ulcer. The acid factor in peptic ulcer has received much attention in recent years,<sup>19</sup> and evidence is accumulating to show that

18. Matthews, W. B., and Dragstedt, L. R.: *Surg., Gynec. & Obst.* 55:265, 1932.

19. Editorial, *J. A. M. A.* 101:859 (Sept. 9) 1933.

it may well be the most important element. The present observations show how a high gastric acidity can be maintained, and suggest that in turn it may of itself initiate inflammatory changes which lead eventually to ulceration, hemorrhage and perforation. Experiments designed to produce this result more regularly are now in progress.

#### SUMMARY

Experimental pyloric stenosis leads to a spontaneous high gastric acidity, and interferes with the normal neutralization of acid introduced into the stomach. Closure of the pylorus in the unanesthetized dog delays or halts, while opening reestablishes, the normally rapid neutralization of gastric acidity. These findings add further evidence supporting the idea that duodenal reflex controls, in a large part, the level of gastric acidity. The application of these findings to a theory of the pyloric control of gastric acidity and to the pathogenesis of duodenal ulcer is commented on.



# ACUTE PANCREATITIS

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The increasing incidence, the relative scarcity of preoperative diagnosis, the high mortality rate and the lack of uniformity in therapy merit the many reports of acute pancreatitis which have appeared in the literature within recent years. All of the clinical bibliography is available by reference to de Takáts and Mackenzie's review.<sup>1</sup> They presented thirty cases of acute pancreatic necrosis in which operations had been performed by nine different surgeons during the years from 1920 to 1930. Two months later McWhorter<sup>2</sup> reported sixty-four cases in which operations had been performed by thirty-two surgeons, all members of the Chicago Surgical Society; in this report he presented a rather extensive review of the literature. The efforts to produce acute hemorrhagic pancreatic necrosis experimentally with a view toward elucidating the etiologic factors involved, have been thoroughly reviewed by Wangenstein, Leven and Manson.<sup>3</sup> It is because we believe that the accumulation of individual experiences may eventually lead to a more comprehensive appreciation of the problems associated with this disease that a report of twenty-two cases of acute pancreatitis encountered by us during the past five years is herein presented.

## CLINICAL ANALYSIS

Our series well exemplifies the infrequency of the preoperative diagnosis of acute pancreatitis. Only five cases were positively diagnosed; two others were believed to be acute pancreatitis or cholecystitis, and another, perforated gastric ulcer or acute pancreatitis. Since it is necessary to observe some particular feature or group of symptoms to make the diagnosis, it is noteworthy that in 63.64 per cent of the cases these indications were absent or inconspicuous. In McWhorter's<sup>2</sup> series a correct diagnosis was made in eight of the sixty-four cases. In order

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From the Koster Clinic, Crown Heights Hospital.

1. de Takáts, G., and Mackenzie, W. D.: Acute Pancreatic Necrosis and Its Sequels, *Ann. Surg.* **96**:418 (Sept.) 1932.

2. McWhorter, G. L.: Acute Pancreatitis; Report of 64 Cases, *Arch. Surg.* **25**:958 (Nov.) 1932.

3. Wangenstein, O. H.; Leven, N. L., and Manson, M. H.: Acute Pancreatitis (Pancreatic Necrosis): Experimental and Clinical Study, with Special Reference to Significance of Biliary Tract Factor, *Arch. Surg.* **23**:47 (July) 1931.

to evaluate adequately all of the clinical aspects in our cases which were diagnosed correctly and to discover the cause for the errors in the remainder we have analyzed the symptomatology and course (table 1).

Although the age incidence varied from 17 to 78 years, 63.64 per cent of our patients were less than 35. This becomes significant when compared to the age incidence in general disturbances of the gallbladder or bile ducts, to which acute pancreatitis is linked clinically and etiologically. While cases are recorded at the age of from 2½ years up, the incidence of this condition in persons under 20 is exceedingly rare. The average age in our series was 38.27 years. McWhorter<sup>2</sup> found an average of 43.3 years; in half of the thirty cases reported by de Takáts and Mackenzie<sup>1</sup> the patients were between the ages of 40 and 60. It is also noteworthy that of our twenty-two patients, 36.36 per cent were men and 63.64 per cent women, which is in accordance with the observation of others.

Examination of the histories elicited symptoms of disease of the biliary tract in 63.64 per cent of the cases. The symptoms appeared from three weeks to ten years prior to the onset of the acute pancreatitis. In the remainder of the cases there was no relevant past history.

The illness prior to operation varied from one day to two weeks. In 40.9 per cent of the cases it occurred within twenty-four hours. In 63.64 per cent there was a sudden onset of pain in the epigastrium or right upper quadrant or both, which was soon followed by vomiting. In the remainder of the cases the onset was less precipitous but similar. Shock and cyanosis occurred in 31.8 per cent, and in these cases the diagnosis was suspected. Transient glycosuria occurred in two cases. No other significant data were observed or obtained by laboratory methods. In five cases tests for pancreatic ferments gave negative results. Hence, clinically, from the sudden onset of pain followed by vomiting, shock and cyanosis the correct diagnosis was made in four cases and was suspected in three others. In a fifth case diagnosed as acute pancreatitis accompanied by obstruction of the common bile duct by calculi and cholangitis of two weeks' duration there was no shock or cyanosis, but the patient was deeply jaundiced. The symptomatology in the remainder of the cases suggested a variety of conditions, such as acute cholecystitis (63.64 per cent), perforated gastric ulcer (14.28 per cent) and acute obstruction of the common bile duct (22.92 per cent).

At operation the pancreas showed the typical inflammatory involvement. Fatty necrosis of the omentum and the typical serosanguineous exudate were observed in fourteen cases (63.64 per cent). Eight cases (36.36 per cent) showed fatty necrosis or the typical serosanguineous exudate. In at least 50 per cent a greenish discoloration of the fat in the gastrohepatic omentum, characteristic of this disease, was noted. In only 18.2 per cent of the cases was the pancreas the only organ in which

TABLE 1.—*Analysis of the Symptomatology*

Case	Age and Sex	Gall-bladder Symptoms	Duration of Present Attack	Location of Pain	Radiation of Pain	Vomiting	Shock	Jaundice	Cyanosis	Sugar in Urine	White Blood Cell Count and Differential <sup>1</sup>	Blood Pressure		Preoperative Diagnosis
												Sys-tolic	Dias-tolic	
1	17 M	None	1 day	Epigas-trium	None	+	+	0	+	0	W.B.C. 22,500 Polys. 88% Lymph. 10% Monos. 2%	112	72	Perforated gastric ulcer
2	33 M	None	4 days	Epigas-trium	None	+	+	0	+	0	W.B.C. 10,500 Polys. 76% Lymph. 22% Monos. 2%	90	60	Acute hem-orrhagic pancreatitis
3	21 M	6 mos.	1 day	Epigas-trium	Right upper quad-rant	+	+	0	+	0	W.B.C. 18,000 Polys. 90% Lymph. 10%	110	70	Perforated gastric ulcer
4	63 M	3 mos.	2 days	Right upper quadrant and epi-gastrium	Back	+	0	0	0	0	W.B.C. 23,000 Polys. 86% Lymph. 14%	110	90	Acute pan-creatitis or cholecystitis
5	33 F	Chole-cystos-tomy 4 yrs. ago	1 day	Right upper quad-rant	Right shoulder and back	+	0	0	0	0	W.B.C. 19,600 Polys. 87% Lymph. 13%	118	72	Common duct obstruc-tion due to calculus
6	32 F	Chole-cystec-tomy 3 yrs. ago	1 day	Right upper quad-rant	Right shoulder and back	+	0	0	0	0	W.B.C. 15,000 Polys. 62% Lymph. 38%	110	60	Common duct obstruc-tion due to calculus
7	27 F	4 mos.	3 days	Epigas-trium	Right shoulder and back	+	0	0	0	0	W.B.C. 15,900 Polys. 93% Lymph. 4% Monos. 3%	130	72	Acute chole-cystitis
8	26 F	6 yrs.	4 days	Right upper quadrant and epi-gastrium	Back	+	0	0	0	0	W.B.C. 12,800 Polys. 92% Lymph. 5% Monos. 3%	122	68	Common duct calculus
9	47 M	None	3 days	Epigas-trium	None	+	+	0	+	1.4%	W.B.C. 11,300 Polys. 91% Lymph. 5% Monos. 4%	90	60	Acute pan-creatitis
10	28 F	2 mos.	3 days	Right upper quadrant and epi-gastrium	Right shoulder and back	+	0	0	0	0	W.B.C. 18,600 Polys. 90% Lymph. 7% Monos. 3%	130	70	Acute chole-cystitis with cholelithiasis
11	68 M	None	2 days	Right upper quadrant and epi-gastrium	Right shoulder	+	0	0	+	0	W.B.C. 33,500 Polys. 87% Lymph. 9% Monos. 4%	122	80	Acute chole-cystitis or pancreatitis
12	32 F	None	3 days	Epigas-trium	Back	+	0	0	0	0	W.B.C. 21,000 Polys. 82% Lymph. 18%	110	80	Acute chole-cystitis
13	27 F	3 wks.	1 day	Right upper quadrant and epi-gastrium	Back	+	0	+	0	0	W.B.C. 15,900 Polys. 92% Lymph. 8%	126	72	Acute chole-cystitis with cholelithiasis

and Course in Twenty-Two Cases of Acute Pancreatitis\*

Temperature; Pulse; Respiration	Fatty Necrosis	Bloody Exudate	Gallbladder Disease	Condition of Pancreas	Operation	Complications	Results	Comment
Temp. 99.8 Pulse 90 Resp. 20	0	+	0	Hemorrhagic necrosis	Capsule of pancreas split and drained	None	Well	Sudden onset; early fatty necrosis on pan- creas only; none on omentum
Temp. 103.8 Pulse 125 Resp. 40	+	+	0	Hemorrhagic necrosis and edema	Capsule of pancreas split and drained; drain to lesser sac	Gener- alized peri- tonitis and paralytic ileus	Death within 5 hrs.	Sudden onset; patient was moribund at time of operation
Temp. 101 Pulse 120 Resp. 24	+	+	Gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Sudden onset; marked edema of gastrohepatic omentum; pathologic report of acute chole- cystitis
Temp. 100 Pulse 120 Resp. 20	+	+	Gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Slow onset with increas- ing pain; "coffee ground" vomitus; path- ologic report of chronic cholecystitis
Temp. 99.6 Pulse 90 Resp. 20	+	0	Gallbladder and common duct calculi	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Slow onset; pains not marked; pathologic report of chronic cholecystitis
Temp. 98.6 Pulse 84 Resp. 20	0	+	Three com- mon duct calculi	Hemorrhagic necrosis and edema	Choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Slow onset with increas- ing intensity of pain; head of pancreas markedly enlarged and necrotic
Temp. 100.2 Pulse 92 Resp. 22	+	+	Gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Sudden onset; head of pancreas swollen and necrotic; pathologic report of chronic cholecystitis
Temp. 99.6 Pulse 92 Resp. 22	+	+	Gallstones	Edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Slow onset; marked edema of entire pan- creas; pathologic report of chronic cholecystitis
Temp. 98 Pulse 150 Resp. 20	+	+	0	Edema	Capsule of pancreas split and drained	Gener- alized within perito- nitis and paralytic ileus	Death within 12 hrs.	Sudden onset; patient in moribund condition at time of operation
Temp. 99.6 Pulse 84 Resp. 20	+	+	Gallstones	Edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Sudden onset; marked edema of entire pan- creas; pathologic report of acute cholecystitis
Temp. 100.4 Pulse 112 Resp. 20	+	+	Chronic cholecystitis; no stones	Edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	Pneu- monia on right side	Well	Slow onset; marked edema of pancreas with a few areas of begin- ning necrosis; patho- logic report of chronic cholecystitis
Temp. 101 Pulse 120 Resp. 25	+	+	Chronic cholecystitis; no stones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	Intra- abdom- inal col- lection	Well	Slow onset; collection broke through wound spontaneously and emptied itself; patho- logic report of chronic cholecystitis
Temp. 98 Pulse 78 Resp. 21	+	+	Gallstones	Edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Sudden onset; marked edema of entire pan- creas; pathologic report of acute cholecystitis

TABLE 1.—*Analysis of the Symptomatology and Con.*

Case	Age and Sex	Gall-bladder Symptoms	Duration of Present Attack	Location of Pain	Radiation of Pain	Vomiting	Shock	Jaundice	Cyanosis	Sugar in Urine	White Blood Cell Count and Differential†	Blood Pressure		Preoperative Diagnosis
												Systolic	Diastolic	
14	36 F	None	4 days	Right upper quadrant and epigastrium	None	+	0	+	0	0	W.B.C. 11,850 Polys. 89% Lymph. 6% Monos. 5%	128	70	Acute cholecystitis with cholelithiasis
15	40 F	7 yrs.	3 days	Right upper quadrant	Right shoulder and back	+	0	+	0	0	W.B.C. 10,150 Polys. 73% Lymph. 24% Monos. 3%	133	78	Acute cholecystitis and common obstruction by stone
16	27 F	2½ yrs.	1 day	Right upper quadrant and epigastrium	Back	+	0	0	0	2+%	W.B.C. 15,200 Polys. 80% Lymph. 20%	128	68	Acute cholecystitis
17	32 F	None	1 day	Epigastrium	Back	+	+	0	+	0	W.B.C. 16,700 Polys. 90% Lymph. 7% Monos. 3%	90	60	Acute pancreatitis
18	78 M	None	1 day	Epigastrium	Back	+	+	0	+	0	W.B.C. 14,400 Polys. 86% Lymph. 10% Monos. 4%	170	55	Perforated gastric ulcer or acute pancreatitis
19	28 M	2 mos.	1 day	Right upper quadrant	None	+	0	0	0	0	W.B.C. 13,500 Polys. 90% Lymph. 5% Monos. 5%	120	82	Acute cholecystitis
20	31 F	6 wks.	2 days	Epigastrium	None	+	+	0	+	0	W.B.C. 14,200 Polys. 82% Lymph. 18%	112	80	Acute pancreatitis
21	56 F	10 yrs.	2 days	Right upper quadrant and epigastrium	Right shoulder and back	+	0	0	0	0	W.B.C. 6,600 Polys. 70% Lymph. 22% Monos. 8%	140	80	Acute cholecystitis with cholelithiasis
22	63 F	Cholecystectomy 2 mos. ago	2 wks.	Epigastrium	None	+	0	+	0	0	W.B.C. 20,000 Polys. 93% Lymph. 7%	150	80	Acute pancreatitis accompanied by common duct obstruction by calculi and cholangitis

\* In each case a Kocher mobilization of the duodenum was performed and the head of the pancreas was palpated for calculi. The mortality was 22.7%.

† W.B.C. indicates white blood cells; Polys., polymorphonuclears; Lymph., lymphocytes, and, Monos., mononuclears.

*in Twenty-Two Cases of Acute Pancreatitis\*—Continued*

Temperature; Pulse; Respiration	Fatty Necrosis	Bloody Exudate	Gallbladder Disease	Condition of Pancreas	Operation	Complications	Results	Comment
Temp. 101 Pulse 132 Resp. 24	+	+	Gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Slow onset; pain gradually increased in intensity; pathologic report of chronic cholecystitis
Temp. 100.8 Pulse 96 Resp. 22	0	+	Cholangitis and gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	None	Well	Sudden onset; marked edema of pancreas; inflammation of common duct with marked enlargement; pathologic report of acute cholecystitis
Temp. 101 Pulse 86 Resp. 22	+	0	Calculi in gallbladder and common duct	Hemorrhagic necrosis	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Sudden onset; incomplete common duct obstruction by calculi; entire pancreas hemorrhagic with beginning necrosis; pathologic report of chronic cholecystitis
Temp. 99.6 Pulse 84 Resp. 24	+	0	Chronic cholecystitis and cholangitis	Edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	Intra-abdominal collection	Well	Sudden onset; marked edema of pancreas; marked inflammation and dilatation of common duct; pathologic report of chronic cholecystitis
Temp. 99.8 Pulse 90 Resp. 28	+	+	Edema of gallbladder wall	Hemorrhagic necrosis	Cholecystostomy; capsule of pancreas split and drained	Evisceration on 3d day following an asthmatic attack	Death within 4 days	Sudden onset; had severe asthmatic attacks in spite of medication; sat up in bed during violent seizure and evisceration occurred; died of generalized peritonitis and cardiac insufficiency
Temp. 99.8 Pulse 88 Resp. 20	+	+	0	Hemorrhagic necrosis and edema	Cholecystostomy; gauze drain to gallbladder and under surface of liver; capsule of pancreas split and drained	Generalized peritonitis and paralytic ileus	Death within 4 days	Sudden onset; pancreas markedly enlarged, filling entire upper part of the abdomen, and entirely necrotic from head to tail
Temp. 101 Pulse 92 Resp. 24	+	+	Chronic cholecystitis with cholelithiasis	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac and gallbladder bed of liver; capsule of pancreas split and drained	Generalized peritonitis and paralytic ileus; cardiac insufficiency	Death within 5 days	Sudden onset; pancreas large and necrotic, especially the head; pain was colicky; pathologic report of chronic cholecystitis
Temp. 101 Pulse 88 Resp. 29	0	+	Gallstones	Hemorrhagic necrosis and edema	Cholecystectomy; choledochostomy; drain to lesser sac; capsule of pancreas split and drained	None	Well	Slow onset; pain gradually increased in intensity; pathologic report of acute cholecystitis; electrocardiogram showed definite coronary disease
Temp. 100.6 Pulse 116 Resp. 24	+	0	Cholangitis and (3) common duct calculi	Hemorrhagic necrosis and edema	Choledochostomy with removal of calculi; drain to lesser capsule of pancreas split and drained	None	Well	Sudden onset of severe pain which was constant and only relieved by morphine; edema of gastrohepatic omentum and common duct

there was apparent involvement. The remainder showed various pathologic disturbances of the gallbladder or the bile ducts. Cholecystitis with concomitant cholelithiasis occurred in 54.54 per cent of the cases; cholecystitis, in 18.2 per cent, and choledocholithiasis per se in 9.09 per cent.

These operative observations, as well as the clinical symptoms in our series, lend emphasis to the experimental studies of the relationship of disease of the biliary tract to acute pancreatitis. The prevalent opinion as expressed by various reviews is to the effect that acute pancreatitis is usually secondary to an involvement of the biliary tract, as a result of which there may occur an intrapancreatic activation of trypsinogen and a subsequent autodigestion of the gland. The exact mechanism is still problematic.

#### DIAGNOSIS

From the foregoing it is obvious that the diagnosis can be made fairly easily in the case presenting an acute onset of knifelike pain in the epigastrium associated with prostration and cyanosis. In ten instances in which pain was localized in the epigastrium, seven patients had an associated shock and cyanosis. The character of the pain is similar to that occurring in a perforated gastric ulcer and hence may be mistaken for it even in the presence of prostration and cyanosis. This diagnosis was made in two of our cases because of an indefinite previous history suggesting gastric ulcer. Hence an adequate past history is of great importance. A less fulminating onset was presented in 36.36 per cent of our cases. It is noteworthy that in thirteen cases improperly diagnosed because of the absence of the typical picture of acute pancreatitis the patients were less than 40 years of age. As shown in the table, the average age in our group was 38.26 years; 63.64 per cent of the patients were less than 35 years of age. Although slightly lower than that reported in the literature, the age incidence generally agrees with that reported by others. In our cases the symptomatology indicated an involvement of the biliary tract. The suggestion is therefore made that for every patient, however young, in whom symptoms indicating an exacerbation of inflammation of the biliary tract is encountered, acute pancreatitis may be the causative factor. This is especially noteworthy when the patient is a male, since acute pancreatitis is just as frequent in males as in females, in contradistinction to the higher incidence of disease of the biliary tract in the latter.

#### PROGNOSIS

The prognosis of a case of acute pancreatitis is generally considered to be grave. Table 2 summarizes the available mortality data previously reported and those in our series. Obviously, many factors may be instrumental in affecting the mortality rate. Some investigators have

stated the belief that conservative treatment will increase the mortality; others, that the reverse is true. In one thousand two hundred and seventy eight patients with pancreatitis treated surgically, Schmieden and Sebening<sup>4</sup> reported a mortality rate of 51.2 per cent. A similar death rate was reported by McWhorter.<sup>2</sup> De Takáts and Mackenzie<sup>1</sup> reported a death rate of 36.6 per cent. Our series showed a mortality rate of only 22.7 per cent. Of the five patients who died postoperatively, two were practically moribund at the time of operation. Another patient (case 18), a man, aged 78, suffered from severe asthmatic seizures. For the first two days following operation the patient was in a fairly good condition. On the third day he had a severe asthmatic attack, during which evisceration occurred, he died within twenty-four hours.

TABLE 2.—*Mortality Data in Cases Previously Reported as Compared with Present Series*

Author	Year	Number of Cases	Mortality, per Cent
Brocq.....	Before 1910	116	78
	After 1910	119	68
Korte.....	1911	103	60
Guleke.....	1924	487	52.2
Schmieden and Sebening.....	1927	1,278	51.2
de Takáts and Mackenzie.....	1932	30	36.6
McWhorter.....	1932	64	54.7*
Koster and Kasman.....	1933	22	22.7

\* Six not operated on, who died.

Two of the more important factors in determining the mortality rate are the severity of the disease and the degree of involvement of the pancreas. We have seen cases in which there was slight edema of the pancreas with slight enlargement and comparatively little necrosis and other cases in which the pancreas was so swollen and edematous that it filled the greater portion of the upper part of the abdominal cavity. In one instance a gland was encountered, the diameter of which in the sagittal plane of the body was 15 cm. Extreme degrees of necrosis involving the entire gland may also be encountered. Between these extremes are all degrees or gradations of severity, and obviously the clinical course varies with the degree and severity of involvement.

We feel definitely that early operation is indicated in all instances in which a diagnosis is made. This is true not only because we believe that the disease can be favorably influenced by operation at an early time but because of the difficulty in accurately making the diagnosis. Pancreatitis may be confused with some diseases in which operation is imperative, such as perforated ulcer.

4. Schmieden, V., and Sebening, W.: *Arch. f. klin. Chir.* 148:319, 1927.



Although we recognize that the value of many of the other procedures combined in what we believe is the radical method of treating this disease may still be open to question, there can be little doubt regarding the favorable influence of decompression of biliary tension by drainage of the biliary tract, and we feel that the earlier this is instituted, the greater will be the likelihood of a favorable termination.

#### TREATMENT

We feel that the surgical treatment of acute hemorrhagic pancreatic inflammation must include the following steps: drainage of the biliary tract; removal of the gallbladder if it is diseased or contains stones; removal of calculi, if present, from the common duct; mobility of the duodenum by the Kocher method for the purpose of more accurately palpating the head of the pancreas in search of calculi in Wirsung's duct; splitting of the capsule of the pancreas for the relief of edema, and drainage of the lesser peritoneal sac and the pancreas. The drainage of the biliary tract is best accomplished: (1) by passing a rubber tube into the common bile duct through the stump of the cystic duct if the gallbladder has been removed for existing disease; (2) by passing a T-tube into the common duct, if it has been opened for the removal of stones, or (3) by a cholecystostomy in the absence of disease of the gallbladder or if, as occasionally occurs, the pancreas is so tremendously swollen as to make the common duct inaccessible. This type of complete operation was carried out in all of the cases in this series, with the exception of case 1, in which the patient was operated on before the procedure was adopted as routine, and cases 2 and 9, in which the patients were moribund on admission and in which it was deemed advisable simply to drain the pancreas. Cholecystostomies were performed on two patients (cases 18 and 19) for the purpose of instituting drainage of the biliary tract. In fifteen of the remaining seventeen patients cholecystectomies were performed with choledochostomy drainage through the stump of the cystic duct or directly by incision into the common bile duct, and in two of the cases (6 and 22) in which the gallbladder was removed previously, drainage was instituted through an incision in the common bile duct, and in each case three calculi of the common bile duct were removed. The operative procedure was carried out as follows:

After laparotomy the gallbladder and bile ducts were carefully examined. In the presence of cholelithiasis and cholecystitis the gallbladder was removed, preferably from below upward, and a catheter was passed into the common bile duct through the stump of the cystic duct and fixed in that position. If the aperture of the cystic duct was too small, the common bile duct was incised, a T-tube introduced directly and the cystic duct stump ligated. If it was deemed unnecessary to remove the gallbladder, the common duct was incised, and a T-tube drainage was instituted, after careful examination had been made to make

certain that no calculi were contained in it or after calculi had been removed. Then the peritoneum to the outer side of the duodenum was bluntly torn; the duodenum was rolled inward toward the median line and the head of the pancreas was exposed retroduodenally. This was carefully palpated for evidence of stone in the duct of Wirsung. If any was found it was removed; if none was found, the gastrohepatic omentum was incised, through which the pancreas was exposed; the capsule of the gland was slit longitudinally, and drainage over the gland was instituted by a cigaret drain or a gauze tamponade, depending on the condition of the pancreas. A cigaret drain was introduced into the lesser sac through the foramen of Winslow, and the abdomen was then closed.

#### SUMMARY AND CONCLUSION

Twenty-two cases of acute pancreatitis with a total mortality rate of 22.7 per cent are reported. Seven of the cases presented the typical picture of a sudden onset of severe epigastric pain followed by continual vomiting and associated with prostration and cyanosis. In two cases presenting a similar picture there was an indefinite previous history of a condition simulating gastric ulcer, which was diagnosed as such. In another case diagnosed as acute pancreatitis accompanied by obstruction of the common duct by calculi and cholangitis of two weeks' duration there was no shock or cyanosis, but the patient was deeply jaundiced. The remainder of the cases presented a less precipitous onset, which was suggestive of acute disease of the biliary tract. Attention is drawn to the fact that this last-mentioned group of cases occurred most commonly in persons under 36 years of age. It is suggested that in making the diagnosis, acute pancreatitis should be suspected in every case which presents a history and symptomatology suggesting an acute exacerbation of disease of the biliary tract. Immediate and complete operation, which includes cholecystectomy if the gallbladder is diseased or contains calculi, probing of the ducts to assure freedom from calculi or to allow for their recognition and removal, drainage of the biliary tract and examination of Wirsung's duct, in addition to treatment of the pancreatic lesion and the associated peritonitis, is advocated.

# CEREBRAL BLOOD FLOW: III AND IV

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## III. CEREBRAL EFFECTS OF OCCLUSION OF THE COMMON OR INTERNAL CAROTID ARTERIES

The efficacy of the circle of Willis in establishing an adequate collateral circulation following occlusion of one of the internal or common carotid arteries has long been a matter of dispute. Advocated as a relatively harmless procedure by some authors, ligation of the carotid artery has been regarded by many others as an extremely hazardous operation, to be undertaken, if at all, in only the most desperate circumstances. One has only to read the following directly contradictory quotations from two eminent American surgeons to appreciate how widely divergent are the opinions on this subject:

Rudolph Matas,<sup>1</sup> in 1911, wrote: "A long and abundant experience with the surgery of the carotid artery, amounting in a period of twenty-five years to over seventy-eight ligations and extirpations of the common trunk and its two branches, has fully convinced me that the risk of fatal intracranial and cerebral complications resulting from an insufficient collateral circulation is not to be underestimated."

On the other hand, Harvey Cushing<sup>2</sup> said: "I have ligated the internal carotid many times without apparent symptoms. I don't now recall any accidents, but there may have been some. I have been careful to restrict these ligations to young or middle-aged persons without vascular disease. . . . Ligation of the common carotid has little, if any, effect on the circulation of head and brain, as anastomoses between the two external carotids are surprisingly free."

Such discrepancies in opinion, which might be multiplied many times from the literature, suggest the need of a critical analytic review of the subject.

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1. Matas, R.: Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries, *Ann. Surg.* **53**:1, 1911.

2. Cushing, H.: Personal communication to the authors, Aug. 6, 1932.

## THE LITERATURE

The literature, particularly of the nineteenth century, abounds in isolated reports of cases of ligation of the carotid artery. Scarcely a volume of the older journals can be examined without finding several. For a long period it was apparently the fashion to publish brief notes on single unusual cases, or to mention them in discussion of the articles of others. In most reports on carotid ligation no mention was made of cerebral complications. Of those which refer to associated cerebral conditions, many are so brief as to make the nature, or even the existence, of a cerebral disorder extremely doubtful. Furthermore, in pre-Listerian days, inevitable infection, with secondary hemorrhage, embolic complications and widespread constitutional phenomena, often added further confusion to the picture.

Fortunately, however, several excellent reviews of that period presented sufficient numbers of cases of ligation of the carotid artery to make a detailed review of most of the early cases unnecessary for the purposes of this article.

According to Garrison,<sup>3</sup> the use of the ligature was first described by Heliodorus (about 100 A. D.) and, shortly thereafter, by Archigenes and Antyllus, the latter describing the proximal and distal ligature for aneurysm which still bears his name.

Although the ancients (as claimed by Chevers,<sup>4</sup> in 1845) must have had occasion sometimes to tie the carotid arteries for hemorrhage, they avoided these vessels whenever possible.<sup>5</sup> We are not aware of a specific account of carotid occlusion until relatively modern times.

In 1765, Jean-Louis Petit<sup>6</sup> described a patient in whom an aneurysm of the right carotid artery had undergone spontaneous healing. The patient apparently had no neurologic symptoms, and died seven years later of apoplexy. The aneurysmal sac was completely obliterated. Baillie<sup>7</sup> described a similar case in 1793, and in the same year, according

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3. Garrison, F. H.: *History of Medicine*, ed. 2, Philadelphia, W. B. Saunders Company, 1917, p. 94. Neuberger, M., and Pagel, J.: *Handbuch der Geschichte der Medizin*, Jena, Gustav Fischer, 1902, vol. 1, pp. 365 and 488.

4. Chevers, Norman: *Effects of Obliteration of the Carotid Arteries on the Cerebral Circulation*, London M. Gaz. 1:1140, 1845.

5. Paulus Aegineta: *The Seven Books of Paulus Aegineta*, translated by Francis Adams, London, The Sydenham Society, 1846, vol. 2, p. 311; translator's commentary, *ibid.* p. 312. *Chirurgie de Paul d'Egine*, translated by René Brian, Paris, Victor Masson, 1855, p. 181.

6. Petit, Jean-Louis, cited by Cutter.<sup>8</sup>

7. Baillie, Matthew: *Tr. Soc. Improvement Med. & Chir. Knowledge*, 1793, p. 122, cited by Cutter.<sup>8</sup>

to Cutter,<sup>8</sup> Hebenstreit<sup>9</sup> mentioned a case in which "the carotid artery was wounded during an operation for the removal of a tumor. The operating surgeon immediately tied the vessel and the patient lived for many years thereafter."

John Abernethy, of St. Bartholomew's Hospital, London, deserves credit for the first adequate description of a ligation of the common carotid artery. Some doubt exists as to the exact date of his operation. The date was given as 1798 by Cutter<sup>8</sup> and Garrison<sup>10</sup> and as 1803 by Pilz<sup>11</sup>; none was given by Norris.<sup>12</sup> Cutter and Pilz referred to the same publication<sup>13</sup> by Abernethy, while Norris referred to a different one.<sup>14</sup> The case was also reported in a later treatise<sup>15</sup> (1811), the only one available to us, but no date was given for the operation. Abernethy's report is very complete and shows careful observation of, and sane reflection on, the patient's condition. The patient had been gored in the neck by an ox, with resulting laceration of the left internal carotid artery and profuse hemorrhage. The common carotid artery was ligated. There developed paralysis of the right side and frequent convulsions on the left side, and the patient died thirty hours after the operation. Postmortem examination revealed extensive "inflammation" of the brain, with "injection" of the vessels and "light brown" cerebrospinal fluid.<sup>16</sup>

In 1803, the common carotid artery was ligated by Fleming,<sup>17</sup> in

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8. Cutter, I. S.: Ligation of the Common Carotid: Amos Twitchell, Surg., Gynec. & Obst. (*Internat. Abstr. Surg.*) 48:1, 1929.

9. Hebenstreit, E. B. G.: *Zusätze zu Benjamin Bell's Abhandlung von den Geschwüren und deren Behandlung*, Leipzig, Weidmann, 1793.

10. Garrison,<sup>3</sup> p. 345.

11. Pilz, C.: Zur Ligatur des Arteria Carotis communis, *Arch. f. klin. Chir.* 9:257, 1868.

12. Norris, N. W.: Statistics of the Mortality Following the Operation of Tying the Carotid Arteries and Arteria Innominata, *Am. J. M. Sc.* 14:13 (July) 1847.

13. Abernethy, J.: *Surgical Observations*, London, T. N. Longman & O. Rees, 1804, p. 193.

14. Abernethy, J.: *Surgical and Physiological Work*, London, Rees, Arne, Brown and Green, 1830, vol. 2.

15. Abernethy, J.: *Surgical Observations on Injuries of the Head*, Philadelphia, Thomas Dobson, 1811, p. 72. It seems probable that this publication is simply an American edition (perhaps revised) of the treatise referred to by Cutter<sup>8</sup> and Pilz,<sup>11</sup> since the quotation made by Cutter appears verbatim in the American publication.

16. Abernethy's shrewd remarks on this case demonstrate an excellent knowledge of cerebral physiology. For example, he wrote with curiosity: "An effusion of blood in the left hemisphere of the brain would affect the opposite side of the body in the same manner that cutting off the supply of blood to the left side appears in this instance to have done" (p. 81).

17. Fleming: *Med.-Chir. Rev.* 3:2, 1827.

England, for hemorrhage, and by Cogswell,<sup>18</sup> in America, in the course of removal of a tumor of the neck. The former's patient lived; the latter's died on the twentieth day, of secondary hemorrhage. Apparently neither patient showed cerebral symptoms.

In 1805, Sir Astley Cooper<sup>19</sup> first ligated the common carotid artery for aneurysm. Hemiparesis developed on the eighth day, and the patient died on the twenty-first day of "inflammation of the sac." The operation was repeated successfully (i. e., the patient survived), and without apparent cerebral symptoms, by Bjerkén<sup>20</sup> in 1807, this time for aneurysm behind the ear, and within a few days of that time, Twitchell<sup>21</sup> tied the common carotid artery for secondary hemorrhage following a gunshot wound. In 1808, Cooper<sup>22</sup> again operated for aneurysm of the common carotid artery, and this time the ligation was successful; the patient recovered, seemingly without complication, and died thirteen years later of apoplexy.

Valentine Mott,<sup>23</sup> in 1818, first ligated the innominate artery, and he ligated the common carotid artery many times in his long and active career.<sup>24</sup> His most important contribution, however, was the application of experimental principles to the subject. In 1831, he reported a careful anatomic study of the injected cervical vessels of a patient in whom one common carotid artery had been ligated three and a half months previously.<sup>25</sup> It is surprising that he failed to mention the intracranial circulation.

In the meantime, another interesting use of ligation of the carotid artery had been proposed and tested. In 1822, Boileau<sup>26</sup> tied one common carotid artery for hemorrhage in a patient known to have epilepsy, and observed that the convulsions ceased "for a considerable time."

18. Cogswell, M. F.: *New England J. Med. & Surg.* **13**:357, 1824.

19. Cooper, Astley: *A Case of Aneurysm of the Carotid Artery*, *Med.-Chir. Tr.* **1**:1, 1812.

20. Bjerkén, cited by Pilz.<sup>11</sup>

21. Twitchell, Amos: *Gunshot Wound of the Face and Neck; Ligature of the Carotid Artery*, *New England Quart. J. Med.* **1**:188, 1843.

22. Cooper, Astley: *Second Case of Carotid Aneurysm*, *Med.-Chir. Tr. London* **1**:222, 1812; *Account of the First Successful Operation Performed on the Common Carotid Artery, for Aneurysm, in the Year 1808, with the Post-Mortem Examination*, in 1821, *Guy's Hosp. Rep.* **1**:53, 1836.

23. Mott, Valentine, cited by Burns: *Successful Ligation of the Innominate Artery*, *J. A. M. A.* **51**:1671 (Nov. 14) 1908, and by Norris,<sup>12</sup> p. 38. The latter also stated that the second innominate ligation was by von Graefe, in 1822, and cited other early ligations.

24. For detailed references to many of these cases, see the reviews of Norris<sup>12</sup> and Pilz.<sup>11</sup>

25. Mott, Valentine: *Description of the Circulation of the Head and Neck in a Case After One Carotid Artery Had Been Tied*, *Am. J. M. Sc.* **8**:45, 1831.

26. Boileau, cited by Norris,<sup>12</sup> p. 32.

Shortly thereafter, McClellan<sup>27</sup> tied the common carotid artery in 1 patient, Becton<sup>28</sup> in 1, and Preston<sup>29</sup> in 5 patients with "epilepsy," or similar neurologic complaints.<sup>30</sup> Subsequently, until after the middle of the century, carotid ligation was employed in many cases of various neurologic disorders, including trigeminal neuralgia, for which the first carotid ligation was done in 1817 by Liston.<sup>31</sup> In 2 of Preston's cases, both common carotid arteries were ligated, a procedure first carried out by Macgill,<sup>32</sup> in 1823.

In the middle third of the nineteenth century, a more critical attitude began to be adopted. Those who affirmed and those who denied the danger of carotid ligation engaged in a spirited controversy, using both clinical and experimental evidence. Mayer<sup>33</sup> performed a series of experiments on six varieties of animals, and concluded that "ligation of a single carotid artery may occasionally derange much the circulation of the cerebral vessels."<sup>33b</sup> On the other hand, Sir Astley Cooper<sup>34</sup> reported a masterful series of experiments on dogs and rabbits, in which he clearly showed that ligation of one or even of both carotid arteries in these animals may cause no major neurologic symptoms, whereas the obstruction of only one vertebral artery almost inevitably results in serious symptoms such as stupor, paralysis, convulsions or disorientation. He made no specific claims of the existence of a similar situation in man, but one is led to think that such was his belief.

Both sides of this controversy were well summarized, in 1845, by Chevers<sup>4</sup> in the first of the notable reviews dealing with the subject. After discussing the experimental and clinical evidence, he expressed the belief that, while ligation of the common carotid artery might often be accomplished with impunity, nevertheless, it was a dangerous procedure which should be employed only if demanded to save the life of the patient: ". . . it would be far better for the surgeon to make up his mind to contend with an active hemorrhage than that he should

27. McClellan: *Am. M. Rev. & J.* 3:328, 1826, cited by Pilz,<sup>11</sup> p. 372. The operation was performed in May, 1826.

28. Becton, F. E: *North Am. M. & S. J.* 4:88, 1827.

29. Preston, J. R.: *Tr. M. & Phys. Soc. Calcutta* 5:345 and 359, 1831; 6:394, 396 and 409, 1832.

30. Several of these cases bear the unmistakable signs of intracranial tumors.

31. Liston, R.: *Cases of Aneurysm*, *Edinburgh M. & S. J.* 16:66, 1820.

32. Macgill, cited by Norris,<sup>12</sup> p. 37.

33. Mayer: (a) *Acta Acad. cæs. Leopold. Carol. nat. cur.* 6:2, 1831; (b) reviewed in *Edinburgh M. & S. J.* 43:487, 1883.

34. Cooper, A.: *Some Experiments and Observations on Tying the Carotid and Vertebral Arteries and the Pneumogastric, Phrenic and Sympathetic Nerves*, *Guy's Hosp. Rep.* 1:457, 1836.

submit his patient to the chance of fatal hemiplegia, even although he believed that chance to be a remote one."

Inman<sup>35</sup> had previously (1844) included in his tables on operative mortality 40 cases in which the carotid artery was ligated, but the first detailed review of the cases reported in the literature was by George W. Norris<sup>12</sup> of Philadelphia. He tabulated 149 cases of carotid ligation. Of that number, 54 patients died as the result of operation. Severe cerebral symptoms appeared early in 25 patients, later (after the third day) in 7. Thirteen died of cerebral involvement. The cerebral symptoms varied from transient hemiplegia to convulsions, coma and death. He included a discussion of 10 cases in which both common carotid arteries had been ligated. In 2 of these both arteries were ligated at the same operation, and both patients died within twenty-four hours. One of the others had severe cerebral symptoms. Included, also, was a discussion of the 9 reported cases in which, up to that time, the innominate artery had been ligated; all the patients had died of secondary hemorrhage. No mention of cerebral symptoms was made. Subscribing entirely to the opinion of Chevers, Norris stated, "Close examination of the cases recorded . . . shows that the operation of deligating the carotid has been too generally looked upon as one of comparatively little danger; an analysis of them proves that serious symptoms frequently follow the mere cutting off of the supply of blood to the brain through this vessel. . . ."

The dangers of carotid ligation were similarly urged by Guthrie<sup>36</sup> and brought out in the reviews of Ehrmann<sup>37</sup> (cerebral symptoms in 47 of 213 cases), Wood<sup>38</sup> (death from "hemiplegia" in 3 of 49 cases) and LeFort<sup>39</sup> (cerebral symptoms in seventy-three of 241 cases). In 1868 appeared the splendid review of Pilz,<sup>11</sup> who reported 586 cases of common carotid ligation, with an operative mortality of 38.5 per cent, and the appearance of cerebral symptoms in 32 per cent. In his lengthy discussion, he pointed out the danger, cited experimental evidence and concluded that the safety of the operation depends on the

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35. Inman, Thomas: *Tables of the Mortality After Operations*, *Lancet* 2:39, 1844.

36. Guthrie, G. J.: *Commentaries on the Surgery of the War in Portugal, Spain, France and the Netherlands*, ed. 6, Philadelphia, J. B. Lippincott Company, 1862; *Lancet* 2:143, 1850.

37. Ehrmann, J.: *Des effets produits sur l'encéphale par l'oblitération des vaisseaux, qui s'y distribuent*, Paris, B. Ballière, 1860.

38. Wood, J. R.: *Early History of Ligature of the Common Carotid Artery, with a Report of the Unpublished Operations in the City of New York*, *New York J. Med.* 3:1, 1857. Two cases are mentioned in this report which may possibly antedate that of Abernethy.

39. LeFort, L.: *Gaz. hebd. de méd.* 11:27, 1864, cited by Pilz.<sup>11</sup>



adequacy of the collateral circulation through the circle of Willis: ". . . von der Integrität jener Strombahnen und dieses Verbindungskreises hängt das Leben, oder wenigstens die volle Gesundheit der Operierten ab" (. . . on the integrity of the channels and connecting circle depends the life, or at least the complete health of the patient).<sup>40</sup>

Eight years later, James Spence<sup>41</sup> wrote: "There is no fear of interrupting the circulation in the brain after ligation of the [common] carotid, though this was formerly considered a great danger. Both carotids may be tied, and yet the circulation will be carried on perfectly." In 1877, Toland<sup>42</sup> stated: "I have ligated the common and external carotids frequently and in every case successfully."

With the teachings of Lister and the advent of aseptic surgery, the operative mortality and the percentages of infection and of secondary hemorrhage all dropped immediately, but the incidence of cerebral complications following carotid ligation remained virtually unchanged. In 1881 and 1882, Weljaminow<sup>43</sup> reported the cases of 33 patients, all operated on with "antiseptic" technic in only 1 of whom cerebral symptoms developed. He also found 20 "antiseptic" operations in the literature without a fatality. Subsequently, however, in a contradictory report from the same clinic, Hagen-Torn<sup>44</sup> stated that 4 instead of 1 of Weljaminow's patients had "indirect brain symptoms." In 1884, after reviewing 800 cases of ligation of the common carotid artery, Friedländer<sup>45</sup> concluded that "er die Ligatur der Carotis zur 'Kupierung akuter und Besserung chronischer Entzündungen' versuchen will" (he [the surgeon] will try ligation of the carotid artery for the arrest of acute and improvement of chronic inflammation). In the same year, Riegner<sup>46</sup> reported a remarkable patient who had one common carotid artery ligated for aneurysm, only to return a year later with an aneurysm of the other. This, too, was ligated. The night of the operation the patient had contralateral hemiparesis which disappeared by morning.

40. Pilz,<sup>11</sup> p. 414.

41. Spence, James: *Lectures on Surgery*, ed. 2, Edinburgh, Adam & Charles Black, 1876, vol. II, p. 483.

42. Toland, H. H.: *Lectures on Practical Surgery*, Philadelphia, Lindsay & Blakiston, 1877.

43. Weljaminow, N. A.: Ein-und-zwanzig Fälle von Unterbindung der Arteria Carotis Communis, *Vrach* 2:749 and 771, 1881; Zwölf Fälle von Unterbindung der Carotis Communis, *ibid.* 3:490, 1882; *abstr.*, *Zentralbl. f. Chir.* 9:787, 1882.

44. Hagen-Torn, O.: Nothwendige Bemerkungen zu den Artikeln über 33 Fälle von Unterbindung der Art. carotis communis von N. A. Weljaminow, *Med. Vestnik*, no. 51, 1883; *abstr.*, *Zentralbl. f. Chir.* 11:430, 1884.

45. Friedländer, J.: Ueber die Ligature der Carotis, *Inaug. Dissert.*, Dorpat, 1881; *abstr.*, *Zentralbl. f. Chir.* 11:429, 1884.

46. Riegner, O.: Doppelseitiges Aneurysma der Carotis communis, durch Unterbindung beider Carotiden geheilt, *Zentralbl. f. Chir.* 11:431, 1884.

In 1892, Zimmermann<sup>47</sup> collected 65 cases of ligation of the common carotid artery reported after 1880. Of these patients 31 per cent died and 26 per cent showed cerebral symptoms. Ten years later appeared Jacobsthal's two reviews<sup>48</sup> of the surgical treatment of aneurysms of the innominate and subclavian arteries, respectively. In both series, the innominate or common carotid arteries, or both, were ligated in 145 patients. Of these groups cerebral symptoms developed in 8. These figures have little significance, however, in view of the high immediate operative mortality. Jacobsthal, although he recognized the danger of cerebral complications, was inclined to minimize it: "Der Collateral-kreislauf bildet sich meist so schnell und reichlich aus, dass Schädigungen in Folge ungenügender Blutzufuhr zum Arm und Gehirn nur selten auftreten" (the collateral circulation generally develops so rapidly and completely that changes resulting from insufficient blood supply to the arms and brain occur only rarely).<sup>49</sup> And again: "Der durch die Aeste der 1. carotis und subclavia, durch Vermittelung der r. Vertebralis und Subscapularis . . . hergestellte Kreislauf erweist sich als genügend." (The circulation formed by the branches of the first carotid and the subclavian arteries by way of the right vertebral and subscapular arteries . . . proves sufficient).<sup>50</sup>

In 1908, Burns<sup>51</sup> reported 46 cases of ligation of the innominate artery. Of these patients, 6 died of "some cerebral lesion."

In 1906, there appeared the first of two opinions directly contradictory to each other, in the French literature. Savariaud,<sup>52</sup> in his review on subclavian aneurysms, stated: "La conclusion . . . c'est que la ligature . . . de la carotide, ou de la vertébrale . . . est une opération grave, très grave même, tant du fait . . . du voisinage des collatérales, qu'à cause des troubles cérébraux engendrés par ces ligatures." (The conclusion is that ligature of the carotid or of the vertebral artery is a serious, even a very serious operation, owing to the

47. Zimmermann, W.: Ueber die Gehirnweichung nach Unterbindung der Carotis Communis, Beitr. z. klin. Chir. 8:364, 1892.

48. Jacobsthal, H.: (a) Beiträge zur Statistik der operativ-behandelten Aneurysm: I. Das Aneurysma der Arteria anonyma, Deutsche Ztschr. f. Chir. 63:550, 1902. (b) II. Das Aneurysma der Arteria Subclavia, *ibid.* 68:239, 1903. Two cases of innominate aneurysm not included in the first review were reported by Page (*Lancet* 1:1004, 1895) and by Ryan (*ibid.* 1:1549, 1895). No mention of cerebral symptoms was made in either case.

49. Jacobsthal,<sup>48b</sup> p. 282.

50. Jacobsthal,<sup>48a</sup> p. 568.

51. Burns: Successful Ligation of the Innominate Artery, J. A. M. A. 51:1671 (Nov. 14) 1908.

52. Savariaud, M.: Le traitement chirurgical des anévrismes de l'artère sous-clavière, Rev. de chir., Paris 34:1, 1906.

proximity of the collateral arteries and of the cerebral disturbances produced by these ligatures.)

Three years after this, Guinard,<sup>53</sup> after stating that he did not believe that either immediate or delayed cerebral complications follow ligation of the carotid artery low in the neck, if the opposite carotid artery and its branches are intact, added: "et alors si on se reporte aux cas de ligature carotidienne pour la cure des anévrysmes, c'est-à-dire chez des malades qui n'ont pas eu d'opérations sur la face, la langue ou le cou, il n'y avait pas d'exemple que le moindre accident cérébral immédiat ait été observé" (if one refers to cases of carotid ligation for the cure of aneurysms in patients who have not had operations on the face, the tongue or the neck, one will find no example of the slightest direct cerebral complication).

Such was the status of opinion when Matas, in 1911, gave the warning of danger quoted in the introduction of this article and when Halsted,<sup>54</sup> in 1914, first advocated the use of metal bands for partially occluding the artery to increase the collateral circulation. Since then, uncomplicated ligations of the common carotid arteries have been reported by Shipley and Lynn<sup>55</sup> (2 cases), Makins,<sup>56</sup> Bond and Mitchell,<sup>57</sup> Telford<sup>58</sup> and Bolt.<sup>59</sup> Griffiths<sup>60</sup> ligated both common carotid arteries without the production of cerebral symptoms. In 2 cases reported by Dandy,<sup>61</sup> it is uncertain whether the common or internal

53. Guinard, A.: Traitement des anévrysmes de la base du cou, *Rev. de chir.*, Paris **39**:229, 1909.

54. Halsted, W. S.: Des partielle Verschluss grosser Arterien, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **43**:349, 1914; *Cylindrical Dilatation of the Common Carotid Artery Following Partial Occlusion of the Innominate and Ligation of the Subclavian*, *Surg., Gynec. & Obst.* **27**:547, 1918.

55. Shipley, A. M., and Lynn, F. S.: Carotid Tumor and Aneurysm of the Internal Carotid, Report of Cases, *J. A. M. A.* **66**:1602 (May 20) 1916.

56. Makins, G. H.: On the Vascular Lesions Produced by Gunshot Injuries and Their Results, *Brit. J. Surg.* **3**:353, 1915.

57. Bond, C. J., and Mitchell: Arteriovenous Aneurysm of the Common Carotid Artery, *Brit. J. Surg.* **3**:307, 1915.

58. Telford, E. D.: Varicose Aneurysm of Left Common Carotid Artery and Internal Jugular Vein, *Brit. J. Surg.* **3**:322, 1915.

59. Bolt, R. F.: Aneurysm at the Termination of the External Carotid Artery and Aneurysmal Varix Between the Bifurcation of the Common Carotid Artery and the Internal Jugular Vein, *Lancet* **2**:1015, 1916.

60. Griffiths, C. A.: Hemorrhage from a Large Vessel in or About the Base of the Skull: Internal Ligation of Both Carotids, *Brit. J. Surg.* **3**:302, 1915. For other such cases, see Locke.<sup>68</sup>

61. Dandy, W. E.: Arteriovenous Aneurysm of the Brain, *Arch. Surg.* **17**:190 (Aug.) 1928. In the text it is stated that the common carotid artery was ligated in both cases (IV and VIII), but in the tables, the internal carotid arteries are said to have been ligated.

carotid artery was ligated. Cerebral complications occurred after ligation of the common carotid artery by Makins,<sup>56</sup> by Madden<sup>62</sup> and by Bland-Sutton.<sup>63</sup>

In the experimental laboratory in recent years, Chauchard and Chauchard<sup>64</sup> studied the "chronaxie" after occlusion of common carotid and vertebral arteries. They found no change an hour and a half after all four vessels were occluded (in dogs). Houssay and Hug<sup>65</sup> found that the maximum period of toleration of complete ischemia of the dog's brain was from eleven to fifteen minutes. As reported later in this article, my colleague and I recently found only slight transient diminution in the volume of flow of blood through the dog's brain following occlusion of one common carotid artery.

The operation of ligation of the internal carotid artery has apparently been employed less frequently. It has been employed or suggested in the treatment of intracranial aneurysms and anomalous arteriovenous communications<sup>66</sup> and as a preliminary measure to extensive operative procedures in the field of its distribution (as in the case of Gluck<sup>67</sup>), but by far the most common condition for which it has been done is the pulsating exophthalmos due, in most cases, to an arteriovenous fistula between the internal carotid artery and the cavernous sinus. The treatment of this condition was admirably reviewed, in 1924, by Locke,<sup>68</sup> who summarized 588 cases, in 38 of which the patients were treated by ligation of the internal carotid artery. Twenty-one and five-hundredths per cent were "cured," 65.79 per cent "improved." Death occurred in 7.9 per cent. Locke advocates careful tests for the adequacy of the collateral circulation by preliminary temporary occlusion of the artery at or before operation (under local anesthesia). He

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62. Madden, F. C.: A Case of Marked Temporary Aphasia After Ligation of the Common Carotid Artery for Traumatic Aneurysm, *Brit. M. J.* **1**:585, 1916.

63. Bland-Sutton, J.: An Aneurysmal Varix of the Internal Jugular Vein and Internal Carotid Artery with Unusual Complications, *Brit. J. Surg.* **3**:490, 1915.

64. Chauchard, A., and Chauchard, B.: Influence de la ligation des artères carotides et vertébrales sur l'excitabilité de l'écorce cérébrale, *Compt. rend. Soc. de biol.* **99**:1572, 1928.

65. Houssay, B. A., and Hug, E.: Action de l'anémie encéphalique sur les centres nerveux et vagues cardiaques, gastriques et intestinaux de la tête isolée, *Compt. rend. Soc. de biol.* **99**:1503, 1928.

66. Cushing, H.: Contributions to the Clinical Study of Intracranial Aneurysms, *Guy's Hosp. Rep.* **73**:159, 1923. Dandy.<sup>61</sup>

67. Gluck: Ueber einen Fall von partiellen Resektion des Felsenbeinpyramide, nebst Bemerkungen über die Ligatur des Carotis interna in Canalis carotica, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **9**:37, 1882.

68. Locke, C. E., Jr.: Intracranial Arteriovenous Aneurysm or Pulsating Exophthalmus, *Ann. Surg.* **80**:1, 1924. Included in this review are 258 cases of common carotid ligation and 21 cases of bilateral carotid ligation.

expressed the belief that if this is done the risk of cerebral anemia is negligible, but that without such tests, ligation of the common carotid artery is preferable (mortality, 1.28 per cent in his series). Dandy<sup>69</sup> recently stated: "This condition (arteriovenous aneurysm between the internal carotid and the cavernous sinus and its sequelae) is easily cured by either partial or complete ligation of the internal carotid artery. After the age of 35, total ligation of the artery is dangerous. A partial occlusion of the artery with a band of fascia is just as effective as a complete ligation."

## COMMENT

To compute accurate percentages of cerebral complications is impossible in view of the incompleteness of many reports and the possible

TABLE 1.—*Age Incidence of Cerebral Complications Following Ligation of the Common Carotid Artery*

Age	Ligation for Hemorrhage	Ligation for Aneurysm or Similar Lesion	Ligation for Other Reasons	Total
10 to 20.....	4	6	0	10
20 to 30.....	14	14	4	32
30 to 40.....	4	4	0	8
40 to 50.....	2	20	2	24
50 to 60.....	4	6	2	12
60 to 70.....	6	6	0	12
70 and over.....	0	2	0	2
Total.....	34	58	8	100

extraneous factors involved in many of the cases. From so large a mass of such variable material, conclusions may be drawn only with great care. However, it is certainly true that occlusion of a common carotid artery will be followed by definite symptoms referable to the brain in a considerable number of cases (probably from 20 to 30 per cent) and that occasionally these symptoms will be serious enough to leave permanent residual damage or, rarely, to produce death.

Certain factors might be expected to influence the frequency of cerebral complications. For example, one might suppose that such complications would occur with greater frequency in cases of advanced cerebral arteriosclerosis, in which the cerebral circulation may already be near its minimum threshold of adequacy and in which the cerebral vessels are able to respond but poorly to the demand for establishment of a collateral circulation, a supposition emphasized in 1908 by von

69. Dandy, W. E.: *Diagnosis and Treatment of Injuries of the Head*, J. A. M. A. **101**:772 (Sept. 2) 1933.

Oppel.<sup>70</sup> This does not prove to be the case, however. In table 1 is shown the age incidence in 100 cases selected at random from the literature in which definite cerebral symptoms occurred following ligation of one common carotid artery. It will be seen that in the majority of cases the patients were under 50 years of age, hence were probably not affected by advanced cerebral vascular disease. Further, if the cases of aneurysm, arteriovenous fistula and similar conditions are left out (for reasons given in the following paragraph), the incidence is far greater in young people. That young people are more liable to trauma is doubtless an important factor in the production of this high percentage.

In a person with an aneurysm of long standing or with similar local vascular disease a compensating collateral circulation might be expected already to have developed, thus making him less liable to cerebral complication if the carotid artery is ligated. But in the 259 cases with preexisting aneurysms or similar lesions reported by Pilz cerebral complications developed in 75 (29 per cent), a figure surprisingly close to the incidence of 32 per cent for his whole series.

There are, then, no criteria on which to base a preoperative prognosis. Danger apparently exists in all cases. The common (or internal) carotid artery should therefore be occluded only in cases in which a greater danger lies in permitting it to remain unoccluded.

#### IV. EFFECT OF OCCLUSION OF THE COMMON CAROTID ARTERIES ON THE VOLUME-FLOW OF BLOOD THROUGH THE DOG'S BRAIN

It is realized that final conclusions regarding man cannot be drawn from experimentation on animals alone, but the similarity of the cerebro-arterial systems in man and the dog will at least allow the making of tentative assumptions. Houssay and Hug,<sup>65</sup> using the "isolated head" preparation, found the greatest time for which the brain might be entirely deprived of blood without loss of the ability to resume its function to be from eleven to fifteen minutes. On the other hand, Chauchard and Chauchard<sup>64</sup> found no difference in chronaxie after occlusion of both common carotid and both vertebral arteries. To our knowledge, no studies have been made on the direct effect on the cerebral circulation of occlusion of these vessels.

#### METHODS

Thirteen experiments were performed on dogs anesthetized by sodium barbital (0.3 Gm. per kilogram of body weight) given intravenously. Each experiment was begun from two to four hours after the injection of the barbital. The arterio-

70. von Oppel, W. A.: Zur operativen Behandlung der Arterio-venösen Aneurysmen, *Arch. f. klin. Chir.* 86:32, 1908.

venous oxygen difference of blood flowing through the brain was determined by the method used in previous studies in this series.<sup>71</sup> The common carotid arteries (and, in some experiments, the vertebral arteries) were exposed and isolated by a midline anterior cervical incision, and were occluded when desired by means of rubber covered "bulldog" clips. Duplicate control determinations were made in all experiments. In nine experiments, one common carotid artery was then occluded, and in eight, another determination was made as quickly as possible afterward. The interval between the occlusion of the artery and the drawing of the samples of blood was usually less than three minutes and never more than five minutes. The venous sample was always drawn first. In seven experiments, subsequent determinations were made at intervals of from thirty to sixty minutes, and again after two hours in four experiments. In three of the experiments, the second common carotid artery was later occluded and the determinations repeated immediately and at longer intervals afterward.

TABLE 2.—*Effect of Occlusion of One and of Both Common Carotid Arteries*

	Determi- nation	Time, Minutes	Arterial Oxygen Content, per Cent by Volume	Venous Oxygen Content, per Cent by Volume	Arterio- venous Oxygen Difference, per Cent by Volume	Change from Control, per Cent, by Volume
Dog Ca; male; weight, 10.2 Kg.; sodium bar- bital 3 Gm. Intra- venously four hours before beginning experiment	I and II (Average)	...	12.90	9.93	2.97	.....
		29	Clip placed on right common carotid artery			
	III	30	12.96	8.12	4.84	+1.87
	IV	60	11.55	8.99	2.56	—0.41
	V	180	12.94	10.09	2.85	—0.12
		290	Clip placed on left common carotid artery			
	VI	295	13.17	7.57	5.60	+2.63
	VII	325	13.42	8.30	5.12	+2.15
	VIII	360	14.51	9.56	4.99	+2.02
	IX	870	12.84	7.15	5.69	+2.72

In four experiments, the effect of occlusion of the vertebral and common carotid arteries was studied, the vessels being occluded one at a time, and each occlusion being followed by a determination of the cerebral arteriovenous oxygen difference.

## RESULTS

*Effect of Occlusion of One Common Carotid Artery.*—In seven of the nine experiments there was an immediate moderate increase in the arteriovenous oxygen difference (1.87, 3.66, 1.57, 1.65, 1.51, 1.27 and 2.40 per cent by volume, respectively); in one experiment there was a diminution of 0.72 per cent by volume. In the remaining experiment, no immediate determination was made. The average immediate change in the eight experiments was an increase of 1.65 per cent by volume. The values in a typical experiment are given in table 2.

71. Pilcher, C.: Cerebral Blood Flow: I. The Effect of Intravenous Administration of Hypertonic and Hypotonic Solutions on the Volume Flow of Blood Through the Brain, *Arch. Neurol. & Psychiat.* 24:899 (Nov.) 1930. Hamm, L., and Pilcher, C.: Cerebral Blood Flow: II. The Effect of Intravenous Injection of Hypertonic and Hypotonic Solutions on the Cardiac Output and Blood Pressure, *ibid.* 24:907 (Nov.) 1930.

In all seven determinations done from thirty to sixty minutes after occlusion of the artery, the direction of change was toward the control level, and in five of the seven the values may be said to have returned to normal (+0.12, +0.16, -0.49, -0.41 and -0.10 per cent by volume, respectively). In the remaining two, values of +1.22 and +1.05 per cent by volume were found, as opposed to +3.66 and

TABLE 3.—*Effect of Occlusion of the Second Common Carotid Artery*

Dog	Time Following Occlusion of Second Carotid, Minutes	Change from Control, per Cent by Volume	Change from Last Determination Before Occlusion of Second Carotid, per Cent by Volume
Ca.....	5	+2.63	+2.75
	35	+2.15	+2.27
	70	+2.02	+2.14
	550	+2.72	+2.84
Cc.....	1	+0.96	+0.84
	30	+4.08	+3.96
Co.....	5	+2.40	±0.00
	50	+4.10	+1.70

TABLE 4.—*Effect of Occlusion of Each Vertebral and Carotid Artery in Series*

Determination	Time, Minutes	Arterial Oxygen Content, per Cent by Volume	Venous Oxygen Content, per Cent by Volume	Arteriovenous Oxygen Difference, per Cent by Volume	Change from Control, per Cent by Volume
I and II (Average)	..	17.16	12.48	4.68	.....
III	20	Clip placed on left vertebral artery			
	30	16.40	11.70	4.70	+0.02
	35	Clip placed on left common carotid artery			
IV	45	16.40	10.55	5.85	+1.17
	50	Clip placed on right vertebral artery			
V	60	16.29	10.61	5.68	+1.00
	65	Clip placed on right common carotid artery			
VI	75	16.71	8.53	8.18	+3.50
	85	All clips removed			
VII	95	15.70	11.21	4.49	-0.19

+1.65 per cent by volume, respectively, immediately after occlusion of the artery. Again, in three of the four determinations made two hours after occlusion of the artery, the arteriovenous oxygen difference was within the limits of normal (+0.97, -0.24 and -0.12 per cent by volume respectively). In the fourth, the value was +2.66 per cent by volume (it had been +1.65 at one minute and +1.05 per cent by volume at thirty minutes after occlusion of the artery). The reason for the increase in utilization of oxygen is not apparent. The mean blood pressure, which was recorded in this experiment, had already risen slowly from a control level of 120 mm. of mercury to 140 mm. at the time of the last determination.



To summarize, occlusion of one common carotid artery resulted usually in an immediate moderate increase in arteriovenous oxygen difference, followed by a fairly rapid return toward, or even slightly below the normal level. Here it was usually maintained for the two hours during which the determinations were made.

*Effect of Subsequent Occlusion of the Second Common Carotid Artery.*—The results are summarized in table 3 and the detailed results in one experiment are given in table 2. Immediately following occlusion of the second carotid artery there was a definite increase in arteriovenous oxygen difference in one experiment and little or no change in the other two. However, later determinations showed a marked and sustained increase.

*Effect of Occlusion of Both Carotid and Both Vertebral Arteries.*—The four experiments gave identical results qualitatively, and the changes closely approximated each other quantitatively. The detailed results in one are given in table 4. Occlusion of one vertebral artery resulted in no appreciable change, but occlusion of one carotid artery was followed by a definite increase in the arteriovenous oxygen difference. Again, occlusion of the second vertebral artery caused little or no change, but when a clip was placed on the second common carotid artery, there was always a marked increase. When all the clips were removed, the arteriovenous oxygen difference returned to a normal or slightly subnormal level.

#### CONCLUSIONS

It must be remembered that any interpretation of the results of these experiments in terms of volume of flow of blood depends on the assumption of a constant consumption of oxygen by the brain throughout the experiments. If the consumption of oxygen is constant, the volume of flow will vary inversely as the arteriovenous oxygen difference. Although there is no reason to believe that the consumption of oxygen of the brain will vary during such experiments, such an assumption must, nevertheless, be purely a tentative one.

If this is borne in mind, it is justifiable to conclude that these experiments indicate the following:

1. Occlusion of one common carotid artery of the dog causes a temporary decrease in the volume of flow of blood through the brain, but this decrease is quickly compensated for, largely, no doubt, through the collateral pathways of the circle of Willis.

2. Occlusion of both common carotid arteries of the dog results in a sustained diminution in the volume of flow of blood through the brain.

3. Occlusion of the vertebral arteries of the dog has comparatively little effect on the cerebral blood flow.

# ABSORPTION OF DEXTROSE FROM THE COLON

W. W. EBELING, M.D.\*

PHILADELPHIA

Within the past few years McNealy and Willems,<sup>1</sup> Pressman,<sup>2</sup> Scott and Zweighaft,<sup>3</sup> Perusse,<sup>4</sup> Burget, Moore and Lloyd<sup>5</sup> and Collens and Boas<sup>6</sup> published data on the absorption of dextrose from the colon which are not entirely in agreement. The subject is of sufficient importance from the clinical point of view to warrant additional studies.

I reported<sup>7</sup> the results of studies on the absorption of dextrose from the colon of the anesthetized dog. It was assumed at that time that anesthesia and the attending operation played little or no part in altering the physiologic process of absorption from the large intestine.

The opportunity arose, however, to study absorption from the colon in the unanesthetized dog through the preparation of a colon loop. One need not, at this time, comment on the advantages or disadvantages of the use of the chronic loop for investigation of intestinal absorption. The results of the studies of Ravdin and his associates<sup>8</sup> on chronic jejunal loops, as well as the results obtained in these experiments, are sufficiently consistent to permit one to conclude that from the chronic loop results may be obtained from which deductions may be drawn as to the activity of the intestinal mucosa. The closed colon loop is comparable to the colon under normal circumstances, in which one end is closed by the rectal sphincters and the other by the ileocecal valve.

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1. McNealy, R. W., and Willems, J. D.: Absorption of Dextrose from Colon: Study of Effects of Chemical Excitants and of Stimulants on Dextrose Enema, *Arch. Surg.* **22**:649 (April) 1931.

2. Pressman, J. J.: *Am. J. M. Sc.* **179**:520, 1930.

3. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following Rectal Administration of Dextrose, *Arch. Int. Med.* **49**:221 (Feb.) 1932.

4. Perusse, G. L., Jr.: *Surg., Gynec. & Obst.* **54**:770, 1932.

5. Burget, G. E.; Moore, P. H., and Lloyd, R. W.: *Am. J. Physiol.* **105**:187, 1933.

6. Collens, W. S., and Boas, L. C.: *Arch. Int. Med.* **52**:317 (Aug.) 1933.

7. Ebeling, W. W.: Absorption of Dextrose from Colon, *Arch. Surg.* **26**:134 (Jan.) 1933.

8. Ravdin, I. S.; Johnston, C. G., and Morrison, P. J.: *Am. J. Physiol.* **194**:700, 1933.

## METHOD

*Preparation of a Chronic Colon Loop.*—The dogs selected for these experiments were of mongrel breeds and weighed from 12 to 20 Kg. The successful preparation of the chronic loop was obtained by a two-stage operation done under aseptic technic. The anesthetic employed for the operation was ether, administered by the open drop method.

The first stage consisted of a midline laparotomy incision, following which the terminal part of the ileum and the cecum, with its attached appendix, were mobilized. A point approximately 4 or 5 cm. from the ileocecal valve was selected for transection of the ileum. The point of transection of the terminal part of the ileum depended primarily on the arrangement of the vascular supply to that portion of the intestine. The division was usually made midway between two of the larger terminal branches of the mesenteric artery. The reason for this care is that the stump of the ileum, which remains attached to the cecum, depends on the blood supply from the mesenteric vessels rather than on that from the colic branches.

The ileum was divided with the actual cautery between two obstructing ligatures of silk. The two raw ends of the ileum resulting from this transection were then buried by means of purse-string sutures of Pagenstecher. The stumps were reenforced by one or two through-and-through seromuscular sutures of similar material. It was often necessary to free the attachment of the appendix alongside the terminal part of the ileum before closure of the distal stump could be completed.

The cecum, with its attached appendix and small stump of ileum, was then allowed to drop back within the abdominal cavity, following which an anastomosis between the ileum and the lower sigmoid flexure was made.

The anastomosis of the terminal part of the ileum to the lower sigmoid flexure was of the side-to-side type and was placed as low on the sigmoid flexure or upper part of the rectum as possible. Anastomotic clamps were employed merely to obstruct the enteric flow in the ileum, and likewise to obstruct the fecal current in the sigmoid flexure during the anastomotic procedure, the contents of the intestine having been milked out prior to the application of the rubber-covered clamps. The incisions in the side of the ileum and sigmoid flexure usually measured about 3 cm. The anastomosis was completed with a double row of fine Pagenstecher sutures, the serosal surfaces being additionally reenforced with occasional interrupted sutures of fine black silk.

A number 12 to 14 soft rubber catheter was passed by an assistant through the anus into the rectum, and was fed through the anastomosis into the terminal part of the ileum to the extent of about 2 or 3 inches (2 or 7.6 cm.). From 6 to 8 inches (15 to 20 cm.) of rubber catheter usually sufficed to reach from the anal orifice up to and through the ileosigmoidostomy opening. From this one could readily determine how far down on the sigmoid flexure the anastomosis had been made.

The abdomen was then closed in layers. Two hundred and fifty cubic centimeters of salt solution was permitted to remain within the peritoneal cavity.

The rectal catheter was usually passed spontaneously after about twenty-four hours. Following immediate recovery, the dogs were returned to the animal house for convalescence before proceeding with the final construction of the colon loop. The animals had diarrhea which frequently persisted for a number of days. In the dogs that survived the initial operation for several weeks, semisoft and later formed stools finally made their appearance.

The mortality in this primary procedure was high, death resulting most frequently from interference with the blood supply of the terminal part of the ileum, owing to the torsion required to bring that portion of the ileum into contact with the lower sigmoid flexure. The dogs that survived this procedure remained apparently healthy, and one in particular, a small wire-haired terrier, gained weight to such an extent that he became rather fat.

The second stage was proceeded with in from three to six weeks following recovery from the primary operation. Laparotomy was performed through an incision of the left rectus muscle. It was surprising to note that in the dogs surviving the initial operation, there were few adhesions within the abdomen. The anastomosis in each instance was cleancut and well formed.

The sigmoid flexure, about 3 cm. proximal to the side of the anastomosis, was ligated at two levels with silk ligatures placed 1 cm. from one another. After the knots were tied down, the ends were permitted to remain long and were held by hemostats which enabled one to mobilize the sigmoid flexure with ease. The mesosigmoid was then carefully separated from its intestinal attachment, special care being taken to control hemostasis without obstructing the larger colic vessels. The sigmoid flexure was cut through with the actual cautery between the two obstructing ligatures, and the stumps were then buried with purse-strings of Pagenstecher. Seromuscular mattress sutures of Pagenstecher were employed to reenforce the closure. Both stumps were brought permanently end-to-end by means of the last placed mattress sutures, the long or free ends of which were used for this purpose.

The inversion of the stump of the distal part of the sigmoid flexure appeared to interfere with the actual anastomosis by somewhat filling the lumen of the sigmoid flexure; however, no difficulty was encountered in the convalescence of the animals from this interference. The rent in the mesentery was not closed, and it appeared to be obliterated in a large part when the two blind ends of the sigmoid flexure were brought adjacent to one another.

The formation of a fistulous opening into the colon loop was carried out as follows: The short distal stump of ileum, which had been separated from the terminal part of the ileum and which had been left attached to the cecum, was brought out of the abdomen through a stab wound to the outer side of the right rectus muscle. Its position was maintained with four interrupted sutures of silk placed at the ends and sides of the stab wound and passed through the serosal and muscular layers of the protruding intestine. Two hundred and fifty cubic centimeters of salt solution was placed in the peritoneal cavity and the laparotomy incision was then closed in layers.

The stump of protruding ileum was opened after several days. The opening thus accomplished permitted ready entry into the colon loop. A small rubber tube measuring about 2 or 3 inches was passed into the colon loop through the enterostomy opening, and the colon loop was gently washed out with warm salt solution.

The rubber tube was permitted to remain in the enterostomy opening for from twenty-four to forty-eight hours, the loop being carefully washed out once or twice during that period, after which the tube was completely removed. The dogs were then returned to the animal house for convalescence. The colon loop was irrigated at frequent intervals during the convalescence and prior to the beginning of the absorption experiments. The animals used in these experiments appeared to remain quite healthy, and their wounds healed without complications.

Absorption experiments were conducted by the double balloon method described by Johnston<sup>9</sup> and used by Ravdin and his associates<sup>8</sup> in their studies on small intestinal loops. A number 14 French soft rubber catheter was perforated freely along that portion which was to lie within the intestinal loop. Two small rubber balloons were placed around this main catheter at a point corresponding to the abdominal wall when the main catheter lay within and throughout the extent of the chronic colon loop. When the two balloons were distended through their separate tubes, the one just within the abdominal loop prevented the catheter from coming out of the loop, while the second, just outside the abdominal wall, prevented the catheter from further entering the loop. Both balloons prevented the loss of fluid from the loop.

Throughout these studies, the dogs were given the routine laboratory diet. Absorption experiments were usually conducted in the afternoon, approximately eighteen hours after the last meal.

For each absorption experiment or series of experiments, the catheter with its balloon was inserted into the loop through the ileostomy opening and fixed in place by distention of the balloons. The loop was then carefully irrigated with warm water until all washings returned clear. It is to be noted that after from twenty-four to forty-eight hours of disuse, a considerable quantity of thick mucus could be washed from the loop. An abdominal binder was usually applied about the animal, through one point of which the end of the main catheter entering the loop protruded. By this method, it was possible quickly to introduce fluids into, or withdraw them from, the colon loop without disturbing the abdominal binder. The abdominal binders were necessary because of the desire of the dogs to chew the rubber catheters and balloons while these were in position.

All the dextrose solutions were freshly made from Bactodextrose. The concentration of the dextrose was determined in all instances by the Benedict method<sup>10</sup> immediately before and at the completion of each experiment.

A measured amount of dextrose solution to be used was introduced into the cleansed and empty loop. The soft rubber catheter, which extended to the end of the loop, was then closed with a Hoffman clamp. At the end of each experiment, the contents of the loop were withdrawn, measured and placed in a volumetric flask, and the loop was then washed out with sufficient water to make up the volume desired for analysis.

#### RESULTS

Three dogs were used for the experiments reported in this paper. Data obtained with the same concentrations of dextrose solution in the same dog were quite similar. While in each instance varying concentrations were not run in series (e. g., 5 per cent for the first hour, 10 per cent for the second hour and 25 per cent for the third hour), in all the experiments reported in this paper the different concentrations were run serially. It was found that there were minor variations for similar concentrations from day to day, although fundamentally, when compared with the changes which occurred with the higher concentrations, they were relatively insignificant.

9. Johnston, G. G.: *Proc. Soc. Exper. Biol. & Med.* **30**:193, 1932.

10. Benedict, S. R.: *The Detection and Estimation of Glucose in Urine*, J. A. M. A. **57**:1193 (Oct. 7) 1911.

*Effect of Varying the Concentration of Dextrose.*—The experiments were planned to test the effect of concentration on the total amount of dextrose absorbed per unit of time. When the concentration was changed only a little, as from 1 to 2.5 per cent, the amount of dextrose absorbed from the 2.5 per cent solution was, as a rule, similar or only slightly higher than that absorbed from the 1 per cent solution. This was at times true with the change from a 2.5 per cent to a 5 per cent solution. The differences between slightly different concentrations were often not as great as those observed by Ravdin and his associates,<sup>8</sup> when a

TABLE 1.—*Effect of Varying the Concentration of Dextrose*

Dog	Date	Time, Hours	Volume In, Cc.	Volume Out, Cc.	Concen- tration In, Gm. per 100 Cc.	Concen- tration Out, Gm. per 100 Cc.	Total In, Mg.	Total Out, Mg.	Total Lost, Mg.
179	3/10/33	1	25	31	5.6	3.8	1,400	1,178	222
	3/10/33	1	25	49	11.2	5.0	2,800	2,450	350
	3/10/33	1	25	72	27.9	8.5	6,975	6,120	855
425	3/10/33	1	25	30	5.8	3.3	1,450	990	460
	3/10/33	1	25	50	11.6	4.3	2,900	2,150	750
	3/10/33	1	25	90	28.7	6.7	7,175	6,000	1,145

TABLE 2.—*Effect of Change in Volume, the Concentration Remaining Constant*

Dog	Time, Hours	Volume In, Cc.	Volume Out, Cc.	Concen- tration In, Gm. per 100 Cc.	Concen- tration Out, Gm. per 100 Cc.	Total In, Mg.	Total Out, Mg.	Total Lost, Mg.
179.....	1	25	23	5.3	3.7	1,325	1,036	289
	1	50	51	5.3	4.3	2,650	2,193	457
	1	25	43	10.6	4.5	2,650	2,160	490
	1	50	96	10.9	4.8	5,450	4,608	842
	1	25	71	26.4	7.9	6,600	5,609	991
	1	50	89	26.1	12.3	13,050	10,947	2,103
	1	50	103	26.3	10.1	13,150	10,908	2,242
425.....	1	25	31	5.3	2.9	1,325	890	426
	1	50	46	5.3	4.8	2,650	2,208	442
	1	25	50	10.6	4.6	2,650	2,300	350
	1	50	73	10.9	6.0	5,450	4,380	1,070
	1	25	75	26.4	7.1	6,600	5,325	1,275
	1	50	103	26.3	10.1	13,150	10,908	2,242
	1	50	103	26.3	10.1	13,150	10,908	2,242

more rapidly absorbing membrane, the jejunum, was used. With the change from a 10 to 20 or 25 per cent solution, there was a decided increase in the absorption of dextrose per unit of time (table 1).

*Effect of Change in Volume, Concentration Remaining Constant.*—With an increase in the volume of fluid introduced into the loop, concentration remaining constant, there was a larger amount of dextrose absorbed. While this difference was most pronounced in the higher (25 per cent) concentrations, it was quite obvious in the lower (from 5 to 10 per cent) concentrations (table 2).

*Effect of Increasing Concentration on Fluid Change.*—With the lower concentrations of dextrose (1, 2.5 and approximately 5 per cent

solutions), little or no increase in the fluid volume occurred, although secretion occurred in the empty loop. On the contrary, with the lower concentrations, there was an actual loss of fluid through absorption. With the higher concentrations (10 per cent), there was a constant increase in the fluid content of the loop, and with the 25 per cent solution, the increase in fluid volume was proportionately greater. These findings are consistent with those which one would expect when hypotonic and hypertonic solutions are used. Although more dextrose is absorbed from the higher concentrations, fluid is drawn into the colon loop from the patient's body stores.

*Effect of a Changing Fluid Volume by Varying Concentration.*—There was a rather constant and rapid decrease in the concentration of the dextrose solution within the loop, in a unit of time, when the 5, 10 and 25 per cent solutions were used. This undoubtedly depended on a relatively constant mobilization of fluid and absorption of dextrose. With lower concentrations (from 1 or 2.5 to 5 per cent), the changes in concentration were not so great. Data obtained from dogs in which hypotonic solutions were used indicated that the colon at times was actually capable of withdrawing water from the hypotonic dextrose solutions more rapidly than it took up the dextrose. When rapid fluid absorption is desired, hypotonic solutions are more desirable.

*Comparison of Rate of Dextrose Absorption in Chronic Colon Loop of Unanesthetized Animal with Rate of Absorption in Isolated Colon of Intact Anesthetized Animal.*—With increasing concentrations of dextrose in the isolated colon of the anesthetized animal, there was an increasing amount of dextrose absorbed. With increasing concentrations in the unanesthetized animals, there was likewise an increase in the fluid volume, as would be expected.

Slightly greater amounts of dextrose were lost for a given concentration in the acute experiments under anesthesia. However, this difference may be explained by the fact that the entire colon was used in the anesthetized dogs and a greater quantity of a given concentration of fluid was employed in each instance. This was shown to result in the absorption of a greater amount of dextrose.

*Rate of Absorption in Chronic Colon Loop as Compared with Rate of Absorption in Chronic Jejunal Loop.*—The highest average absorption of dextrose from the chronic colon loop (dog 425), when 25 cc. of a 5.8 per cent solution was placed within the loop, was 460 mg. in one hour. The nearest figures of Ravdin and his associates<sup>8</sup> gave an absorption of 260 mg. in one instance when 20 cc. of a 5.3 per cent solution was used, and 607 mg. in another instance when 20 cc. of a 5.6 per cent dextrose solution had been placed in the chronic jejunal loop for but fifteen minutes. The highest loss of dextrose from an

approximately 25 per cent solution when 50 cc. had been placed in the colon loop for one hour was 2,790 mg. When 50 cc. of approximately 30 per cent dextrose solution had been placed in the jejunal loop, 2,200 mg. was lost in fifteen minutes. This comparison further substantiates the fact that the colon will absorb dextrose at a much slower rate than the jejunum.

#### COMMENT

The preparation of a chronic colon loop, as outlined, carried with it a high operative mortality, but once the loop was completed, it offered a means of studying absorption from the colon in the unanesthetized animal whose intestinal loop had its nerve, blood and lymphatic supply intact. This type of chronic loop provides a method for repeated study in the same animal over a long period of time. On the basis of sections removed from one colon loop and from comparison of repeated studies, it appears that these loops remained histologically and physiologically normal over an indefinite period.

It was shown that the rate of absorption of dextrose from the colon increased slightly with increasing concentrations up to 5 per cent, which approximates an isotonic solution. With increasing concentrations beyond this point, there was a decided increase in the rate of dextrose absorbed. It was further shown that with an increase in the volume of solution, concentration remaining constant, there was a decided increase in the dextrose absorbed.

Comparing these data with those obtained on absorption of dextrose from the entire and isolated colon in the anesthetized animal, it is evident that anesthesia per se made but little difference in the conduct of the colon as a physiologic unit. When compared with the results obtained on chronic jejunal loops by Ravdin and his associates,<sup>8</sup> as well as the results obtained in the low ileac loop in the anesthetized animal, it was shown that the colon absorbs dextrose at a much slower rate than does the ileum or jejunum.

These studies substantiate the results of my previous investigation on the absorption of dextrose solution from the colon. It appears that the amount of dextrose absorbed from the colon is too small to be of any considerable clinical value.

#### CONCLUSIONS

1. The chronic colon loop affords a simple and efficient method for the study of absorption of dextrose solutions from the colon.
2. The rate of absorption of dextrose depends primarily on the concentration of the solution used and the quantity placed within the colon.



3. These studies further substantiate the view that the colon as a means of introduction of dextrose into the body mechanism is inadequate for clinical needs, and, further, actual harm may result from the use of hypertonic solutions, owing to withdrawal of water.

NOTE.—In an article by Cutting just published (Cutting, R. A.: Absorption of Dextrose and Water by the Small Intestine and the Colon, *ARCH. SURG.* 29: 643 [Oct.] 1934) exception was taken to my earlier studies because they were conducted "under anesthesia and after extensive intra-abdominal surgical manipulations." The experiments reported in the present paper are devoid of this criticism; yet the conclusions reached are essentially the same as those previously reported. The present data are the only ones reported on experimental animals with a chronic condition.

# END-RESULTS OF OPERATION ON THE THYROID GLAND

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Surgical intervention is considered the proper treatment for the various types of thyroid disease; still one must admit that there is much to be desired in this field. It is difficult to evaluate completely the results obtained, even under the best conditions, owing to the numerous variable factors which may be encountered in procuring the data.

Crile<sup>1</sup> reported from the Cleveland Clinic that 86.3 per cent of more than 12,000 patients treated for hyperthyroidism were able to resume their former occupation in less than a year after the operation. Moore<sup>2</sup> reported cures in 82.7 per cent of persons with exophthalmic goiter, in 88.9 per cent of those with adenomatous goiter and in 51 per cent of those with secondary exophthalmic goiter (toxic adenoma). What constitutes a cure he did not state, and therefore it is difficult to know on what basis the cures may be evaluated. From the Portland Clinic, Joyce<sup>3</sup> reviewed the results in 1,066 patients treated by operation, most of whom had exophthalmic goiter or toxic adenoma. Eighty per cent of the patients were well and strong and able to work. His observations were made from three to six years after thyroidectomy. Rapid and irregular heart action was the most common residual symptom. There was recurrence of the goiter in 3.6 per cent of those with adenomatous goiter and in 5.7 per cent of those with hyperplastic goiter. In a small series, Dunhill<sup>4</sup> found that 90 per cent of the patients were able to return to a normal mode of living after thyroidectomy for hyperthyroidism. Collier and Potter,<sup>5</sup> reviewing the cases in University Hospital, Ann Arbor, found that complete rehabilitation occurred in 91.4 per cent of the patients with exophthalmic goiter, in 95.6 per cent of those with toxic adenomas and in 94.5 per cent of those with nontoxic adenoma. How-

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1. Crile, George: *Diagnosis and Treatment of Diseases of the Thyroid Gland*, Philadelphia, W. B. Saunders Company, 1932, chap. 39; *Thyroidectomy: Its Indications and End-Results*, *Practitioner* **125**:661, 1930.

2. Moore, J. C.: *Subtotal Thyroidectomy: Deductions from 1,700 Cases*, *Northwest Med.* **31**:118, 1932.

3. Joyce, Thomas M.: *Thyroid Surgery at the Portland Clinic*, *Ann. Surg.* **94**:563, 1931.

4. Dunhill, T. P.: *Toxic Goiter*, *Practitioner* **125**:672, 1930.

5. Collier, F. A., and Potter, E. B.: *End-Results of Thyroidectomy*, *Ann. Surg.* **94**:568, 1931.

ever, when these apparently satisfactory results were analyzed further, it was found that only 48.3 per cent of the patients with exophthalmic goiter and toxic adenoma had no residual symptoms. Residual cardiac symptoms were found to a greater or less degree in 26.8 per cent of those with exophthalmic goiter and in 34.4 per cent of those with toxic adenomas. It was also pointed out that the patients who were operated on earliest in the course of the disease were more free from residual symptoms after a period of years than those who had the condition for a longer time before surgical intervention was attempted.

Many patients who show only a few residual symptoms and are able to resume their former economic station are, nevertheless, definitely handicapped as a result of the remaining symptoms.

In reviewing Richter's results following thyroidectomy for hyperthyroidism Elliott<sup>6</sup> found that 70 of 100 patients were well, whereas the remaining 30 were aware of some disability. Definite evidence of visceral injury as a result of hyperthyroidism was present in 41. He stated that the failure to obtain ideal results may be attributed largely to the failure to make an early diagnosis, thereby neglecting surgical therapy until damaging and frequently permanent visceral symptoms occur.

Alfred H. Noehren,<sup>7</sup> from the Buffalo clinic for the treatment of thyroid disease, reported the results of 100 consecutive operations three months postoperatively, and concluded that between 80 and 90 per cent of the patients were cured at that time. This period of observation is too short to determine cures, but it is interesting to note that his percentages are comparable to those obtained by other investigators who studied their results over longer periods of time.

#### MATERIAL FOR THE PRESENT INVESTIGATION

A clinical study of all patients with goiter operated on at the Minnesota General Hospital from January 1918 to January 1931 was undertaken. There were 527 patients. Sixty-nine per cent were female and 31 per cent were male. Patients with toxic goiter constituted approximately 80 per cent. The exact frequency of each type was:

	No. of Cases	Per Cent
Exophthalmic goiter.....	292	55.6
Toxic adenoma .....	121	22.8
Nontoxic adenoma.....	98	18.6
Colloid goiter.....	7	1.3
Cancer .....	5	0.9
Thyroiditis .....	4	0.8

6. Elliott, Charles A.: The Results of Thyroidectomy for Hyperthyroidism from the Internist's Standpoint, *Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America* 6:519, 1930.

7. Noehren, Alfred H.: Results of Thyroidectomy, *Ann. Surg.* 93:1045, 1931.

Comments on the symptoms of the various thyroid diseases are so readily available that they have not been included here. It is interesting to note, however, that the average duration of symptoms before operation in the various diseases is somewhat variable, as can be observed in those cases on which sufficient data were obtainable.

Type	No. of Cases	Duration of Hyperthyroidism, Months
Exophthalmic goiter.....	261	20.1
Toxic adenoma.....	112	34.4

Type	No. of Cases	Duration of Goiter, Months
Nontoxic adenoma.....	82	66.5
Colloid goiter.....	5	109.4
Cancer .....	5	51.2

The average duration of the cases of exophthalmic goiter in which complete cures were reported was less than that of those in which cures were not satisfactory. This did not appear to be true of the cases of toxic adenoma, but the discrepancy may have been due to the fact that there were not enough cases in this group to make conclusions from them reliable. Percentage of improvement in relation to the duration of symptoms was as follows:

	No. of Cases	Duration of Symptoms, Months
Exophthalmic goiter		
100% improved.....	28	10.9
75 to 99% improved.....	69	18.0
0 to 74% improved.....	15	53.0
Toxic adenoma		
100% improved.....	9	29.3
75 to 99% improved.....	25	24.3
0 to 74% improved.....	7	22.8

The response of the pulse rate and basal metabolic rate to the administration of iodine preoperatively was interesting. In the patients with exophthalmic goiter the pulse rate and basal metabolic rate showed a definite decline except in a few instances. In the group with toxic adenoma, this reaction was not as uniform. Some patients showed a definite decline in the pulse rate, but others showed an increase or no change. These facts are being investigated from a statistical standpoint, and will be dealt with in a subsequent article.

#### END-RESULTS

In an effort to determine the end-results obtained, follow-up letters were sent to all patients, and subsequent examinations were made whenever possible. Many could not be traced, owing to change of address or to lack of response to the letters. Two hundred and ten

replies were received. Only a few patients (27) returned for personal observation. The results observed in that group corresponded well with those reported in response to the questionnaire, but in view of the fact that there was not a sufficient number of cases from which to draw accurate conclusions, they were left out of consideration in the tabulations, in order to avoid the possibility of confusing the end-results.

An effort was made to estimate the percentage of improvement in each case on the basis of information received in answer to the questionnaire. The patients who reported no residual symptoms were graded 100 per cent improved. The others were graded by estimating from the response to the questionnaire, much as one would study an examination paper, the percentage of improvement in each case. These estimations are, of course, not free from error, and are subject to the same criticism that one may attach to the results from any questionnaire. Figures were used in an attempt to establish something more tangible than is expressed by the words excellent, good, fair, poor and rehabilitated, which are fraught with as much possibility for variation as would be expected from the numerical estimations.

The questionnaires were examined by Dr. Adam Smith (internist), and it was found that his grading corresponded, on the whole, very closely with mine. He estimated the same number of patients as cured, but graded each of the improved patients as having approximately 5 per cent more disability. This seems to indicate that the questionnaires have been properly evaluated, for in all probability the estimations of two men could not approach one another more closely. The degree of improvement was as follows:

	No. of Cases	Per Cent	
Exophthalmic goiter .....	125		
Perfect (100% improved).....	30	24.0	} 81.6% satisfactorily rehabilitated
Excellent (85 to 99% improved)..	60	48.0	
Good (75 to 84% improved).....	12	9.6	
Fair (50 to 74% improved).....	5	4.0	
Poor (1 to 49% improved).....	3	2.4	
No improvement .....	12	9.6	
Dead subsequently .....	3	2.4	
Toxic adenoma .....	51		
Perfect .....	10	19.6	} 76.4%
Excellent .....	23	45.1	
Good .....	6	11.7	
Fair .....	0	0.0	
Poor .....	3	5.8	
No improvement .....	4	7.8	
Dead subsequently .....	5	9.8	
Nontoxic adenoma .....	23		
Perfect .....	5	21.7	} 73.7% satisfactorily rehabilitated
Excellent .....	8	34.7	
Good .....	4	17.3	
Fair .....	1	4.3	
Poor .....	0	0.0	
No improvement.....	4	17.3	
Dead subsequently.....	1	4.3	

It is evident from the preceding record that although only a small percentage of the patients obtained perfect results, a large group obtained satisfactory results and could be classified as cured, rehabilitated or able to resume their former economic station. In the patients graded from 75 to 90 per cent improved many of the residual symptoms were of minor importance and did not appreciably incapacitate the patient. Cardiac palpitation, dyspnea on exertion, weakness of the legs and tremor of the hands were the residual symptoms most frequently observed. They were minimal in many cases.

Eighty-seven per cent of those who responded to the questionnaire said they were better after the operation than before. On closer inspection of the individual questions it was discovered that some persons were only slightly better. Some of the questions were completely ignored. A tabulation of the answers revealed the following results:

Do you feel better, worse or the same as before your operation?		
Better .....	184	87.6%
Worse .....	8	3.8%
The same.....	16	7.6%
No reply.....	2	0.9%
Is your nervousness more, less or the same as before your operation?		
More .....	191	4.2%
Less .....	161	76.6%
The same.....	33	15.7%
No reply.....	7	3.3%
Does your heart pound or flutter?		
Yes .....	79	37.1%
No .....	102	48.5%
No reply.....	29	13.8%
Have you gained or lost weight or is it the same as before your operation?		
Gained .....	169	80.4%
Lost .....	13	6.1%
The same.....	9	4.2%
No reply.....	19	9.4%
Do you perspire too easily?		
Yes .....	57	27.1%
No .....	105	50.0%
No reply.....	48	22.8%
Is your appetite good, poor or too good?		
Good .....	127	60.4%
Poor .....	12	5.7%
Too good.....	22	10.4%
No reply.....	49	23.3%
Do you become short of breath when walking upstairs?		
Yes .....	88	41.9%
No .....	83	39.5%
No reply.....	37	17.6%
Do you have any shaking of your hands?		
Yes .....	46	21.9%
No .....	119	56.6%
No reply.....	45	21.4%

Do you have any diarrhea?

Yes .....	16	7.6%
No .....	184	87.6%
No reply.....	10	4.7%

Has your goiter grown since your operation?

Yes .....	17	8.0%
No .....	157	74.7%
No reply.....	36	17.1%

Do you notice any weakness in your legs now?

Yes .....	70	33.3%
No .....	119	56.6%
No reply.....	21	10.0%

Are you stronger, weaker or the same as before your operation?

Stronger .....	135	64.2%
Weaker .....	27	12.8%
The same.....	32	15.2%
No response.....	16	7.6%

Is the scar on your neck rough or smooth?

Rough .....	19	9.0%
Smooth .....	142	67.6%
No reply.....	49	23.3%

Have you noticed any change in your voice since the operation?

Yes .....	32	15.2%
No .....	63	30.0%
No reply.....	115	54.7%

Are your eyes more prominent, less prominent or the same as before your operation?

More .....	13	6.1%
Less .....	28	13.3%
The same.....	39	18.5%
No reply.....	130	61.8%

Have you any other ailments? If so, what?

Yes .....	92	43.8%
No .....	65	43.8%
No reply.....	53	25.2%

By further investigation of the response to the last question it was shown that of the patients whose improvement was less than 75 per cent, 70.7 per cent had other ailments, whereas of those whose improvement was graded 75 per cent or more, only 38.2 per cent had other ailments. This may be significant only to the extent that it suggests that some of the symptoms which had been attributed to goiter, perhaps by both the physician and patient, may have had their origin elsewhere.

The other ailments were variable, and included gynecological disorders, disease of the gallbladder, "dyspeptic" troubles, intestinal disorders, frequent headaches, dizzy spells and fainting spells. Anything which could not be attributed definitely to the thyroid condition was included among the other ailments. A check on the other ailments has not been included in this study.

The hospital mortality for the entire group was 2.2 per cent. This is a little higher than was found in a more recent series, which showed

1.36 per cent during the years from 1928 to 1931.<sup>8</sup> The difference may be accounted for, however, by the fact that the entire group includes patients operated on before the use of iodine had become established and also includes patients operated on by seventeen surgeons over a period of twelve years. Crile reported an operative mortality of 0.86 per cent. Goetsch<sup>9</sup> had an operative mortality of 1.25 per cent in a series of 1,755 cases. He remarked that the fatal outcome was not related to the type of operation, for it occurred after ligation, lobectomy or bilateral subtotal thyroidectomy. It was his opinion that the injudicious use of iodine was a contributing factor in increasing the risk, by making the patient refractory to iodine.

An estimation of the results based on the amount of thyroid tissue remaining was not made, because there were so many surgeons involved and the possibility of error in matching one surgeon's "third of a normal-sized lobe" with that of another would be too great. Until the amount can be more accurately expressed such an estimation will be without value.

#### CONCLUSIONS AND SUMMARY

It appears that the results from operation on the thyroid are by no means ideal. It seems safe to state that approximately 25 per cent of the patients will receive perfect results, 60 per cent more will obtain satisfactory results, and the remaining 15 or 20 per cent will remain more or less incapacitated and may even require further therapy.

Eighty-seven per cent of those who responded to the questionnaire indicated that they were improved. The subsequent course of those with poor results has not been accurately ascertained. Some have returned for a second operation and others have received roentgen-ray therapy, but most of them have not been followed up, owing to the lack of adequate follow-up methods at the time of operation.

The shorter the duration of hyperthyroidism the more satisfactory were the results following thyroidectomy.

The administration of iodine caused a definite improvement, with a reduction in the pulse rate and basal metabolic rate, in patients with exophthalmic goiter. Patients with toxic adenoma failed to show uniformly an improvement after the administration of iodine.

Only a few patients (11 per cent) reported no improvement.

More accurate diagnosis and evaluation of the other symptoms might aid in the elimination of surgical treatment for those patients who suffer from ailments not related to thyroid disease which may be the underlying factor in their disability.

8. Rice, Carl O.: Comparison of the Goiters from the State of Minnesota with Those from the Canton of Bern, Switzerland, *West. J. Surg.* **40**:506, 1932.

9. Goetsch, Emil: Mortality in Goiter Operations, *Ann. Surg.* **94**:167, 1931.



The results obtained in this clinic from roentgen-ray treatment of exophthalmic goiter are being investigated by Dr. Adam Smith. Anticipating these results after observing many of the cases, it appears that with the exception of the time factor the end-results from surgical or roentgen-ray therapy will be found to approach each other closely. However, the time factor may be the most important feature in the cure of exophthalmic goiter as indicated in this article, because during the six to nine months which are required to obtain results by roentgen-ray therapy the patient may become definitely more toxic. Therefore the choice of surgical intervention in preference to roentgen-ray therapy may be an important factor in determining the end-result to the best advantage of the patient.

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# INFLUENCE OF EXPOSURE TO COLD AND OF DEPRIVATION OF FOOD AND WATER ON THE DEVELOPMENT OF SHOCK

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My earlier experiments<sup>1</sup> and those of Parsons and Phemister<sup>2</sup> showed that severe trauma to an extremity causes a sufficient loss of red blood cells and of blood plasma into the injured tissues to account for the associated decline in blood pressure. These studies were performed at room temperature on animals which had not been deprived of food and water. The present experiments were carried out to determine the effects of cold and of the deprivation of food and water on the minimum loss of blood necessary to produce death. Loss of blood was produced in some instances by the removal of blood through a cannula that had been placed in the femoral artery and in others by injury to the muscles.

## METHODS

All of the animals were anesthetized and exhibited no evidence of pain. A cannula that was connected to a mercury manometer was introduced into the femoral or carotid arteries in order that the blood pressure might be determined. In the experiments in which the effects of bleeding were studied, whole blood equaling 1 per cent of the body weight was removed from the femoral artery at one hour intervals until death occurred. In the experiments in which the effects of injury to the muscles were studied, the trauma was produced by striking one of the posterior extremities repeated blows with a hammer. Following death in the latter experiments, the difference in the weights of the traumatized and non-traumatized posterior extremities was determined by a method that has been described previously.<sup>1</sup> Hematocrit determinations were performed in some of the studies.

In some of the experiments in which the influence of exposure to cold was studied, pentobarbital sodium was used as the anesthetic. The pentobarbital sodium was introduced intravenously in the dosage of 30 mg. per kilogram of body weight. If normal animals are given this amount of pentobarbital sodium, they usually regain consciousness in approximately four hours. In several instances it was necessary to supplement the initial injection by additional pentobarbital sodium in

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This study was aided by a grant from the Fluid Research Fund of the Rockefeller Foundation.

1. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* 20:959 (June) 1930.

2. Parsons, E., and Phemister, D. B.: Hemorrhage and Shock in Traumatized Limbs, *Surg., Gynec. & Obst.* 51:196, 1930.

order to maintain deep anesthesia. In other experiments, large doses of morphine were used as the anesthetic. In the studies in which an extremity was traumatized, the morphine was supplemented by ether anesthesia while the trauma was being produced. In a few experiments, sodium barbital (0.3 Gm. per kilogram of body weight administered intravenously) was used as the anesthetic. The temperature of the room was approximately 4 C. (39.2 F.). The rectal temperature of the animals was determined frequently.

In the experiments in which the influence of deprivation of food and water was studied, sodium barbital (0.3 Gm. per kilogram of body weight administered intravenously) was used as the anesthetic. No food or water was given during the forty-eight hours preceding the injection of the barbital. One hour following the introduction of the barbital, blood was removed from the femoral artery, or an extremity was traumatized.

#### EXPERIMENTAL RESULTS

*Exposure to Cold.*—Pentobarbital Sodium as the Anesthetic: Twenty control experiments were performed in which the effects of exposure to cold under pentobarbital sodium anesthesia were studied. No bleeding was produced. In ten of the experiments, additional pentobarbital sodium was administered during the course of the observations. All of the animals with the exception of four died. The length of time that the remaining sixteen lived varied from one hour and forty-five minutes to fifteen hours. The average period of survival was five hours and forty-six minutes. The terminal decline in the arterial blood pressure in all the experiments was abrupt. The blood pressure usually remained at a high level until a short time before death. Associated with a marked slowing of the respiratory rate, a rise in blood pressure occurred, and this was followed in a short while by a decline of the blood pressure to zero. In several experiments the respiratory movements ceased about ten minutes before the heart stopped beating. The rectal temperature at the time of death in the various experiments varied from 21.5 to 32.8 C. (70.7 to 91 F.). The average terminal temperature in the sixteen experiments in which death occurred was 25.85 C. (78.53 F.). There was an increase in the concentration of the red blood cells in all of the experiments in which hematocrit determinations were performed. In one experiment the percentage of red blood cells increased from 40 at the time of the control studies to 56 at the time of death, an increase of 40 per cent of the original hematocrit determination. In another the increase was from 49.6 to 66.6 per cent. The smallest increase that was observed in an experiment in which death resulted was from 40 to 43.6 per cent. The results of these experiments are given in table 1.

Nineteen experiments were performed in which blood was removed from the femoral artery of animals which had been given pentobarbital sodium and exposed to cold surroundings. Additional pentobarbital

TABLE 1.—The Effects of (1) Exposure to Cold, (2) Exposure to Cold and Hemorrhage and (3) Exposure to Cold and Trauma (Pentobarbital Sodium Anesthesia)

Cold and Hemorrhage										Cold and Trauma									
Cold Control					Change in Hematocrit, per Cent*					Difference in Weight					Change in Hematocrit, per Cent*				
Ex-periment	Time Lived	Termi-nal tem-perature	Char-acter of Decline in Blood Pressure	Change in Hematocrit, per Cent*	Ex-periment	Time Lived	Termi-nal tem-perature	Char-acter of Decline in Blood Pressure	Change in Hematocrit, per Cent*	Ex-periment	Time Lived	Termi-nal tem-perature	Char-acter of Decline in Blood Pressure	Change in Weight	Ex-periment	Time Lived	Termi-nal tem-perature	Char-acter of Decline in Blood Pressure	Change in Hematocrit, per Cent*
1	5 hrs. 35 min.	23.8	Abrupt		1	5 hrs. 35 min.	20.6	Gradual		1	3 hrs. 20 min.	23.0	Abrupt	1.0	1	3 hrs. 20 min.	23.0	Abrupt	
2	3 hrs. 16 min.	25.4	Abrupt		2	5 hrs. 10 min.	?	Gradual		2	3 hrs. 20 min.	24.3	Abrupt	1.5	2	3 hrs. 20 min.	24.3	Abrupt	
3	5 hrs. 10 min.	32.8	Abrupt		3	5 hrs. 35 min.	?	Gradual		3	52 hrs.	17.8	?	6.1	3	52 hrs.	17.8	?	
4	15 hrs. 10 min.	?	?		4	0 hrs. 35 min.	23.3	Gradual		4	4 hrs. 55 min.	20.0	Gradual	5.2	4	4 hrs. 55 min.	20.0	Gradual	
5	4 hrs. 10 min.	24.3	Abrupt		5	0 hrs. 45 min.	20.4	Gradual		5	3 hrs. 45 min.	25.6	Abrupt	1.8	5	3 hrs. 45 min.	25.6	Abrupt	
6	4 hrs.	?	Abrupt		6	5 hrs. 45 min.	20.4	Gradual		6	2 hrs. 50 min.	30.2	Fairly	2.0	6	2 hrs. 50 min.	30.2	Fairly	
7	2 hrs. 25 min.	26.0	Abrupt		7	7 hrs. 20 min.	35.1	Gradual		7	6 hrs. 15 min.	25.0	Still up	5.0	7	6 hrs. 15 min.	25.0	Still up	
8	3 hrs. 40 min.	23.0	Abrupt		8	2 hrs. 30 min.	28.2	Abrupt		8	(8 hrs.)	(37.0)	(4.7)		8	(8 hrs.)	(37.0)	(4.7)	
9	3 hrs. 16 min.	26.3	Abrupt		9	0 hrs. 35 min.	28.0	Gradual		9	(24 hrs.)	(50.3)	(4.4)		9	(24 hrs.)	(50.3)	(4.4)	
10	5 hrs.	22.0	Moderately abrupt		10	0 hrs.	28.1	Gradual		10	8 hrs. 13 min.	20.0	Gradual	4.7	10	8 hrs. 13 min.	20.0	Gradual	
11	1 hr. 45 min.	30.7	Abrupt	+25	11	0 hrs. 55 min.	27.2	Gradual		11	4 hrs. 55 min.	27.7	Abrupt	3.6	11	4 hrs. 55 min.	27.7	Abrupt	
12	2 hrs. 35 min.	24.0	Abrupt	+24	12	1 hr. 30 min.	30.0	Abrupt		12	1 hr. 50 min.	28.7	Abrupt	2.0	12	1 hr. 50 min.	28.7	Abrupt	
13	(30.8)	(30.8)	Still up	(+21)	13	5 hrs. 25 min.	29.0	Gradual		13	2 hrs. 15 min.	30.0	Abrupt	2.8	13	2 hrs. 15 min.	30.0	Abrupt	
14	Recovery	21.5	Abrupt	+40	14	4 hrs. 30 min.	25.5	Gradual	+11	14	7 hrs. 45 min.	30.0	Fairly	4.0	14	7 hrs. 45 min.	30.0	Fairly	
15	4 hrs. 50 min.	22.2	Abrupt	+34	15	0 hrs. 40 min.	32.8	Gradual	0	Aver.	8 hrs. 27 min.†	25.52	gradual	3.31	Aver.	8 hrs. 27 min.†	25.52	gradual	
16	0 hrs. 15 min.	?	Abrupt	?	16	5 hrs. 30 min.	24.5	Gradual	— 3										
17	(42.0)	(42.0)	Still up	(+ 0)	17	3 hrs. 35 min.	25.3	Gradual	— 3										
18	Recovery	24.0	Abrupt	+ 0	18	3 hrs. 45 min.	27.2	Abrupt	+ 2										
19	(36.2)	(36.2)	Still up	(+ 3)	19	5 hrs. 40 min.	31.8	Gradual	—21										
20	Recovery	(35.8)	Still up	(+10)	20	5 hrs. 10 min.	28.37	Gradual											
Aver.	5 hrs. 40 min.	25.85																	

\* The hematocrit value was calculated by determining the difference in the hematocrit readings during the control period and that at the time of death and dividing this difference by the reading for the control period.

† This includes the experiment in which the duration was fifty-two hours.

sodium was given to six of the animals. As has been stated, whole blood equaling 1 per cent of the body weight was removed each hour until death occurred. The duration of the experiments varied from one hour and thirty minutes to seven hours and twenty minutes. The average duration of the experiments was five hours and sixteen minutes. The decline in the blood pressure was gradual in sixteen of the nineteen experiments. In the remaining three, the blood pressure remained at a high level until shortly before death, when an abrupt decline took place. The loss of blood that was associated with death in these three experiments was small. In one experiment it equaled 2 per cent of the body weight; in the second, 1 per cent, and in the third, 3 per cent. The total quantity of blood that was removed in the various experiments varied from 1 to 7 per cent of the body weight. The average amount removed in the nineteen experiments equaled 4.86 per cent of the body weight or approximately one half of the estimated blood volume. The rectal temperature of the animals at the time of death varied from 24.5 to 35.1 C. (76.1 to 95.2 F.). The animal which tolerated hemorrhage best had the highest temperature at the time of death. Hematocrit determinations were performed frequently in six of the experiments. In all instances, an increase in the concentration of the red blood cells was noted during the early part of the experiments. When the blood pressure fell to a low level, dilution of the red cells occurred. At the time of death, the hematocrit reading was approximately the same as it had been during the control period in four of the experiments. In one experiment a slight concentration persisted, and in the remaining experiments there was a definite dilution. The animal in which the marked terminal dilution of the red blood cells occurred had the highest temperature at the time of death. The figures in the table that refer to hematocrit readings are concerned only with a comparison of the determinations during the control period and those at the time of death. The results of these experiments are given in table 1.

Fourteen experiments were performed in which one of the posterior extremities of animals anesthetized by pentobarbital sodium and exposed to cold surroundings was traumatized. Additional pentobarbital sodium was subsequently injected in five of the experiments. Two animals in which the temperatures were essentially normal and in which the mean arterial pressures were greater than 100 mm. of mercury were killed eight and twenty-four hours, respectively, after the beginning of the experiments. The difference in the weights of the posterior extremities was 4.7 per cent of the body weight in one of the experiments and 4.4 per cent in the other. The results of these experiments are not included in the average in the tables. The duration of the remaining twelve experiments varied from one hour and fifty minutes to fifty-

two hours. The average duration was eight hours and twenty-seven minutes. Excluding the experiment in which the animal lived for fifty-two hours, the average duration was four hours and twenty-nine minutes. In seven of the experiments, death was preceded by a slowing of the respiratory movements and an abrupt decline in the arterial pressure from a fairly high level to zero. It was in these experiments that the difference in the weights of the traumatized and nontraumatized extremities was least. The difference in the weights of the traumatized and nontraumatized extremities varied from 1 to 6.1 per cent of the body weight. The average difference equaled 3.31 per cent. The temperature at the time of death in the different experiments varied from 20 to 30.2 C. (68 to 86.3 F.). The average rectal temperature at the time of death was 25.52 C. (77.93 F.). Following the traumatization, there was an increase in the concentration of the red blood cells in the five experiments in which hematocrit determinations were performed. A dilution of the red blood cells occurred shortly before death in two of the experiments, and the hematocrit readings were approximately the same at the time of death in these two experiments as they had been during the control period. That a marked increase in the concentration of the blood is not a necessary feature of the fatal results in these animals was shown in one experiment in which the hematocrit reading reached during the control period was 28.7 and the highest reading reached during the experiment was 33.9. In another experiment the maximum alteration in the hematocrit readings was from 33.8 to 38.8. The greatest alteration in the hematocrit readings that was observed was from 39.4 during the control period to 47.5 at the time of death. The figures in the tables that have to do with hematocrit readings refer only to a comparison of those obtained during the control period and at the time of death. The results of these experiments are given in table 1.

**Sodium Barbitol as the Anesthetic:** Experiments in which sodium barbitol was used as the anesthetic instead of pentobarbital sodium were also performed, and the effects of exposure to cold, of cold and hemorrhage and of cold and trauma were studied. The results were similar to those obtained when pentobarbital sodium was used as the anesthetic. They differed in that the period of survival of the animals was somewhat shorter and in that the amount of hemorrhage tolerated was slightly less.

**Morphine as the Anesthetic (Supplemented by Ether in Cases of Trauma):** The effects of exposure to cold were studied in four experiments in which morphine was used as the anesthetic. Death occurred nine hours following the beginning of one of the experiments. The respiratory rate a short time before death was 3 per minute. The terminal temperature was 16.8 C. (62.2 F.). The duration of another of

TABLE 2.—*The Effects of (1) Exposure to Cold and Hemorrhage and (2) Exposure to Cold and Trauma (Morphine Anesthesia) Supplemented by Ether During Traumatization*

Supplemented by Ether During Traumatization)											
Cold and Hemorrhage					Cold and Trauma						
Experi- ment	Time Lived	Terminal Temperature	Change in Hematoerit, per Cent*	Amount Bled, per Cent of Body Weight	Character of Decline in Blood Pressure	Experi- ment	Time Lived	Terminal Temperature	Change in Hematoerit, per Cent*	Difference in Weight of Extremities, per Cent of Body Weight	Character of Decline in Blood Pressure
1	6 hrs. 5 min.	22.6	-38.3	6.0	Gradual	1	6 hrs. 30 min.	18.6	+ 2.1	3.18	Gradual
2	6 hrs. 30 min.	23.0	-35.2	6.5	Gradual	2	7 hrs. 20 min.	20.2	+16.2	3.41	Gradual
3	6 hrs. 30 min.	27.6	-42.3	6.5	Gradual	3	10 hrs.	20.0	.....	5.24	Gradual
4	6 hrs. 40 min.	28.9	-22.3	6.5	Gradual	4	6 hrs. 40 min.	23.6	-15.9	5.86	Gradual
5	6 hrs. 30 min.	20.5	-17.8	6.4	Gradual	5	7 hrs. 30 min.	16.0	-23.1	5.22	Gradual
Average	6 hrs. 27 min.	25.7	-30.8	6.38	Gradual	Average	7 hrs. 36 min.	19.7	.....	4.58	Gradual

\* The hematocrit value was calculated by determining the difference in the hematocrit readings during the control period and at the time of death and dividing this difference by the reading for the control period.

\* The hematocrit value was calculated by determining the difference in the hematocrit readings during the control period and at the time of death and dividing this difference by the reading for the control period.

the experiments was fifteen hours. The terminal temperature was not determined. Observations were discontinued in the remaining two experiments after twenty-three hours. The rectal temperatures at the end of this time were essentially normal. These experiments indicate that exposure to cold is tolerated better by animals narcotized by morphine than by those anesthetized by pentobarbital sodium or barbitol.

Five experiments were performed in which hemorrhage and exposure to cold were studied in animals anesthetized by morphine. The average duration of the experiments was six hours and twenty-seven minutes; the average rectal temperature at the time of death was 25.7 C. (78.2 F.), and the average amount of blood removed in terms of body weight

TABLE 3.—Studies on (1) Bleeding and (2) Trauma in Animals Deprived of Food and Water for Forty-Eight Hours

Bleeding			Trauma		
Experiment	Duration	Amount Bled, per Cent of Body Weight	Experiment	Duration	Difference in the Weight of the Posterior Extremities, per Cent of Body Weight
1	3 hrs. 5 min.	4.00	1	5 hrs. 12 min.	4.47
2	4 hrs. 22 min.	5.00	2	8 hrs. 19 min.	4.64
3	4 hrs. 10 min.	5.00	3	7 hrs. 50 min.	5.77
4	2 hrs. 10 min.	3.00	4	6 hrs. 4 min.	4.50
5	4 hrs. 45 min.	5.50	5	6 hrs.	4.57
6	5 hrs.	6.00	6	5 hrs. 55 min.	3.32
7	3 hrs. 55 min.	4.50	7	3 hrs. 10 min.	3.23
8	4 hrs. 50 min.	5.50	8	4 hrs. 20 min.	4.43
9	2 hrs.	2.75			
Average	3 hrs. 49 min.	4.58	Average	5 hrs. 51 min.	4.45

was 6.38 per cent. The concentration of the red blood cells increased during the early part of four of the five experiments, but a marked terminal dilution occurred in all instances. The decline in the blood pressure in all of the experiments was gradual. The results of these experiments are given in table 2.

Five experiments were performed in which trauma and exposure to cold were studied in animals anesthetized by morphine alone except for the addition of an inhalation ether anesthetic during the time in which the trauma was being produced. The average duration of the experiments was seven hours and thirty-six minutes; the average rectal temperature at the time of death was 19.7 C. (67.5 F.), and the average difference in the weights of the traumatized and nontraumatized extremities as expressed in terms of body weight was 4.58 per cent. A dilution of the red blood cells occurred in some experiments, and a concentration in others. The decline in the blood pressure in all of the experiments was gradual. The results of these experiments are to be found in table 2.



*Deprivation of Food and Water.*—As has been stated, the animals were deprived of food and water for forty-eight hours preceding the experiments, and sodium barbital was used as the anesthetic. Nine experiments were performed in which at one hour intervals blood equaling 1 per cent of the body weight was removed from the femoral artery. This was continued until death occurred. The average duration of these experiments was three hours and forty-nine minutes. The average amount of blood removed in the nine experiments equaled 4.58 per cent of the body weight. The results of the experiments are enumerated in table 3.

In eight experiments, one of the posterior extremities was traumatized. The average length of time that the animals lived following the traumatization was five hours and fifty-one minutes. The average difference in the weights of the traumatized and nontraumatized extremities was 4.45 per cent of the body weight. The results of these experiments are to be seen in table 3.

#### COMMENT

*Influence of Exposure to Cold.*—Concerning the relationship of the external temperature to shock, Cannon<sup>3</sup> stated:

That the incidence and severity of shock are in some way related to the coldness of the surroundings of the wounded man seems well established. Members of shock teams working in the A.E.F. during the summer and fall of 1918 reported the strikingly larger number and the greater severity of the cases of shock in the cold, wet months of the fall, September and October, as contrasted with the cases seen during the fighting in the warm weather of July and August.

Observations such as these prompted Bayliss and Cannon<sup>4</sup> to perform experiments on the effects of low temperatures. It was found that the blood pressure of an animal anesthetized by ethyl carbamate (urethane) could be greatly reduced by cold surroundings. They stated:

This effect, however, was chiefly due to slowing of the heart beat, the pressure falling with the rate. When the animal was warmed, there might be complete recovery of the normal pressure. On the other hand, probably some additional effect is produced besides that on the heart, for, after slight hemorrhage, cooling resulted in a fall of pressure which was not restored when the animal was warmed.

It has been shown<sup>5</sup> that dogs and cats may recover after the body temperature has reached 19 C. (66.2 F.). An instance of complete recovery in a person whose temperature had fallen on exposure to 24 C. (75.2 F.) is recorded.<sup>5</sup>

3. Cannon, W. B.: *Traumatic Shock*, New York, D. Appleton & Company, 1923, p. 90.

4. Cannon,<sup>3</sup> p. 93.

5. Britton, S. W.: *Extreme Hypothermia in Various Animals and in Man*, *Canad. M. A. J.* 22:257, 1930.

The present experiments were performed primarily in order to obtain a comparison of the effects of hemorrhage outside the body, as from the exposed femoral artery, and of hemorrhage into the injured tissues of an extremity when the animals were exposed to a low temperature. The short period of survival of the animals which were simply given pentobarbital sodium and exposed to cold was surprising. The average rectal temperature at the time of death was 25.85 C. (78.53 F.). This is approximately what one would anticipate in view of previous work. In this connection, Barbour<sup>6</sup> stated: “. . . chemical regulation must break down rapidly, for Storm van Leeuwen has shown that cooling tends to reduce the reflex irritability of the spinal cord. This reduction becomes very marked at a body temperature of 26°, which may explain why this temperature approximates the lowest compatible with life.” In two of the control experiments, the rectal temperature was more than 30 C. (86 F.) at the time of death, and it is not known why the subjects succumbed. The alterations in the blood pressure in these experiments were somewhat different from those found by Bayliss and Cannon.<sup>4</sup> There was a slow, gradual decline in the pressure in their experiments. In the present experiments, the arterial pressure usually remained at essentially the normal level until shortly before death, when it rose slightly and then fell abruptly. This was associated with a slowing of the heart rate, but death seemed to be due to respiratory failure, as the respirations ceased before the heart stopped beating. It is well known that exposure to cold is associated with an increase in the concentration of the red blood cells. This finding was confirmed in the present experiments, in most of which the increase in the concentration was marked. The slowing of the circulatory flow that is associated with a large increase in concentration of the blood is probably partially responsible for the fatal outcome in these experiments. That it could not be wholly responsible is demonstrated in one experiment in which the hematocrit readings were 40 during the control period and 43.6 at the time of death. The circulatory flow is also slowed by an increase in the viscosity of the blood. Denning and Watson<sup>7</sup> found that the viscosity is increased 3 per cent with a fall of 1 degree C. (1.8 degree F.) and that the temperature factor is more effective the larger the number of corpuscles present.

In the experiments in which blood was removed from the femoral artery of animals anesthetized by pentobarbital sodium, the average temperature at the time of death was 3 degrees higher than that of the

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6. Barbour, H. G.: The Heat-Regulating Mechanism of the Body, *Physiol. Rev.* **1**:299, 1921.

7. Denning and Watson: The Viscosity of the Blood, *Proc. Roy. Soc., London*, s.B **78**:353, 1906.

control studies, despite the fact that there was a difference of only thirty minutes in the average duration of the two groups of experiments. The amount of blood removed was less than 5 per cent of the body weight or approximately one half of the total blood volume in only five of the nineteen experiments in which death was produced by bleeding. In three of these experiments, death was associated with an abrupt decline in the blood pressure from a high level to zero, just as was found in most of the control studies. When animals which are not exposed to cold are bled each hour an amount equaling 1 per cent of the body weight, death usually occurs after the fifth or sixth bleeding or after a little more than half of the estimated blood volume has been removed. Hence, it is to be noted in experiments of the duration reported here that exposure to cold does not usually lessen greatly the tolerance to hemorrhage. Had smaller amounts of blood been removed at hourly intervals, it is likely that the total hemorrhage withstood would have been less. This, however, did not seem to be a desirable or necessary experimental procedure, since the duration of life in the studies in which whole blood was removed was approximately the same as that in the experiments in which the animals were simply given pentobarbital sodium and exposed to cold. Hemorrhage and exposure to cold were associated with an increase in the concentration of the red blood cells which became less marked or was replaced by a dilution when the blood pressure fell to a low level. The increase in the concentration was not nearly so marked as that observed in the control experiments. In brief, the control experiments on exposure to cold under pentobarbital sodium anesthesia and those in which blood was removed under similar conditions were of approximately the same duration; a more marked increase in the concentration of the red blood cells was found usually in the control experiments, and the decline in the arterial blood pressure in the experiments on hemorrhage was usually gradual, while in the control studies there was an abrupt terminal decline in the pressure.

There was a great variation in the results of the experiments in which trauma was produced under pentobarbital sodium anesthesia. One of the animals lived fifty-two hours; the difference in the weights of the traumatized and nontraumatized extremities equaled 6.1 per cent of the body weight, and the temperature at the time of death was 17.8 C. (64 F.). As an example of the other extreme, one animal lived one hour and fifty minutes, the difference in the weights of the two posterior extremities was 2 per cent of the body weight, and the terminal temperature was 28.7 C. (83.7 F.). Two of the animals in which traumatization was produced were killed eight and twenty-four hours, respectively, following the beginning of the experiments. It is interesting that the arterial blood pressure had not declined much in these

experiments, that the temperature was essentially normal, and that the difference in the weights of the extremities indicated a loss of almost half of the blood volume into the injured area. The survival period of the traumatized animals corresponded more closely to that found in the control experiments than to that encountered in the experiments in which whole blood was removed. That is to say, the shortest and the longest survival periods were found in the control experiments and in the experiments in which trauma was produced. The average rectal temperature at the time of death of the traumatized animals was slightly lower than that found in the control experiments and more than 3 degrees lower than that found in the studies on hemorrhage. In six of the experiments the difference in the weights of the traumatized and nontraumatized extremities amounted to at least 4 per cent of the body weight. These figures correspond closely to those that were found<sup>1</sup> when traumatization was performed without exposure of the animal to cold. However, in the remaining experiments, the loss of fluid into the injured area was not by itself sufficient to cause death. The decline in blood pressure was gradual in the experiments in which the loss of fluid was great enough to account for death, whereas there was an abrupt terminal decline in the pressure in the experiments in which the loss of fluid was smaller. The behavior of the blood pressure in the latter experiments was similar to that encountered in the control studies of pentobarbital sodium anesthesia. The amount of fluid that was lost into the injured area did not bear any constant relationship to the temperature at the time of death. That an increase in the concentration of the red blood cells was not the main factor in causing death in the experiments in which the local loss of fluid was small was shown in two experiments in which no marked concentration occurred. One is then faced with the question as to what caused the death of the animals in which the part of the circulating blood volume that escaped into the injured area was not great. A comparison of the results of these experiments with those obtained in other experiments in which morphine was used as the anesthetic indicates that the pentobarbital sodium anesthesia in the presence of cold was the main cause.

In the dosages that were used in the present experiments, the anesthesia that is produced by sodium barbital is more profound and of longer duration than that produced by pentobarbital sodium. It is likely for this reason that the animals anesthetized by barbital and exposed to cold survived for a shorter period of time and withstood hemorrhage less well than those in which pentobarbital sodium was used.

That exposure to cold may cause the death of animals anesthetized by morphine was demonstrated by the fatal outcome in less than sixteen hours in two of the four experiments. However, in studies of the

duration of those experiments in which the effects of hemorrhage and of trauma were noted, exposure to cold did not greatly alter the results. These experiments were of approximately seven hours' duration. The decline of the blood pressure in these experiments was gradual, while in many of the experiments in which pentobarbital sodium or barbital was used it was abrupt. The average loss of blood resulting in death in the experiments in which blood was removed was 6.38 per cent of the body weight or more than half of the total blood volume. A greater loss than this is not tolerated by animals which are not exposed to cold. The average difference in the weights of the traumatized and nontraumatized extremities in the five experiments in which injury was produced was 4.58 per cent of the body weight. It is to be noted that this figure is definitely less than that obtained in the experiments on hemorrhage. This difference may be due to the fact that ether as well as morphine was used in the experiments in which trauma was instituted. The more rapid decline in the temperature in the experiments on trauma may have exerted some effect. The average terminal temperature in the experiments on hemorrhage was 25.7 C. (78.3 F.), while that in the studies on trauma was 19.7 C. (67.5 F.).

*Influence of Deprivation of Food and Water.*—A comparison of the results found in the present experiments with those obtained previously in experiments<sup>8</sup> in which food and water were allowed indicates that depriving animals of food and water for forty-eight hours does not lessen greatly the loss of fluid from the blood stream that is associated with death. This applies both to the experiments in which whole blood was removed from the femoral artery and to those in which one of the posterior extremities was traumatized. The average quantity of blood removed from the femoral artery resulting in death was approximately the same as the average difference in the weights of the traumatized and nontraumatized extremities in the experiments in which injury was produced.

#### SUMMARY

Animals anesthetized by pentobarbital sodium were exposed to a temperature of approximately 4 C. (39.2 F.). The blood pressure and rectal temperature were determined frequently, and in some instances hematocrit readings were performed. Death occurred in most of the experiments. The average survival period was approximately six hours. The average terminal rectal temperature was 25.85 C. The blood pressure remained at a high level until shortly before death. Associated

8. Johnson, G. S., and Blalock, A.: Experimental Shock: IX. A Study of the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells, Arch. Surg. 22:626 (April) 1931. Blalock.<sup>1</sup>

with a slowing or cessation of the respiratory movements, the blood pressure rose and fell abruptly to zero. A rather marked increase in the concentration of the red blood cells was found.

In experiments in which whole blood equaling 1 per cent of the body weight was removed at one hour intervals from the femoral arteries of animals anesthetized by pentobarbital sodium and exposed to cold, the average period of survival was five hours and sixteen minutes; the average temperature at the time of death, 28.87 C. (83.97 F.), and the average quantity of blood removed, 4.86 per cent of the body weight. The decline in blood pressure was usually gradual rather than abrupt. In three experiments the terminal decline in blood pressure was abrupt, and a relatively small amount of blood had been withdrawn. Associated with the bleeding and the exposure to cold there was an increase in the concentration of the red blood cells. When the blood pressure reached a low level, a dilution usually occurred.

The results of the experiments in which exposure to cold and trauma were studied were variable. The average temperature at the time of death was 25.52 C. (77.94 F.). In some of the experiments, the difference in the weights of the traumatized and nontraumatized parts was sufficiently great to explain the cause of death on the basis of loss of local fluid alone. In these experiments there was a gradual decline in the blood pressure. In other experiments only a small part of the blood volume was lost into the injured extremity. The terminal decline in the blood pressure in these experiments was abrupt. The traumatization of the extremities was followed by an increase in the concentration of the red blood cells.

The results of experiments in which shock was produced during exposure to cold in animals anesthetized by morphine were quite different. Morphine alone was used as the anesthetic in the experiments on hemorrhage, while morphine supplemented by ether was used in those on trauma. The average loss of blood resulting in death in the experiments on hemorrhage was 6.38 per cent of the body weight or more than half of the total blood volume. The average loss of fluid into the injured extremity in the experiments on trauma was 4.58 per cent of the body weight. The average terminal temperature in the experiments on hemorrhage was 25.7 C. (78.3 F.) and in those of trauma, 19.7 C. (67.5 F.). The decline in the blood pressure in these experiments was gradual rather than abrupt.

It is to be noted from the experiments concerned with the influence of exposure to cold on the development of shock as a result of hemorrhage and of trauma that the results are dependent largely on the depth of anesthesia and the time of exposure.

Experiments were also performed in which the influence of the deprivation of food and water on shock produced by hemorrhage and by trauma was studied. Food and water were not allowed during the forty-eight hours preceding the beginning of the studies. The animals were anesthetized by barbital. It was observed that the loss of blood which resulted in the death of the animals was not much less than that found in experiments in which the animals were not deprived of food and water. The weight of the blood that was removed from the femoral artery in the experiments in which death was produced by bleeding was approximately the same as the difference in the weights of the injured and uninjured extremities in the experiments in which death was caused by trauma.

# THERAPEUTIC USE OF CONCENTRATED ANTISTREPTOCOCCUS SERUM OF NEW YORK STATE DEPARTMENT OF HEALTH

IN CRYPTOGENIC STREPTOCOCCEMIA AND OSTEOMYELITIS  
OF CHILDREN

ADELE E. SHEPLAR, M.D.  
MARTHA JANE SPENCE, M.A.  
AND  
WARD J. MACNEAL, M.D.  
NEW YORK

In our series of twenty-six patients treated with the special concentrated antistreptococcus serum of the laboratory of the New York State Department of Health there were five patients with generalized or metastatic infection without a clinically recognizable entry portal. These patients were brought under observation in the hospital after invasion of the blood stream had taken place. It is uncertain whether the site of the initial invasion could or could not have been recognized at an earlier time by a competent observer. All five of these patients were children, aged 2 weeks, 27 months, 31 months, 43 months and 5 years, respectively.

## REPORT OF CASES

CASE 1 (chart 1).—A. M., a boy, born on April 5, 1933, breast fed, had a high fever fourteen days after birth accompanied by swelling of the left thigh. On admission to the hospital five days later, on April 24, there was a marked swelling of the anterior portion of the left thigh with a slight excoriation in the inguinal folds on both sides. The left hip joint was immobile, and there appeared to be flaccid paralysis of the left knee and ankle. The entire limb was discolored by purple mottling. Aspiration of the swollen thigh on April 25 yielded about 2 cc. of bloody fluid from which hemolytic streptococci were obtained on culture. The next day the thigh was incised, but only a thin fluid was discovered. Roentgenologic study did not reveal any changes in the bone. On May 1 a blood culture was taken, and on the same day yellowish-brown pus was evacuated from a fluctuating swelling on the left buttock. This pus contained streptococci, and the blood culture yielded one colony of the same microbe per cubic centimeter of blood.

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This work was made possible by a grant from the Josiah Macy Jr. Foundation. From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

The patients whose records are utilized in this paper were treated in the clinical services of the following physicians: Dr. R. H. Dennett, Dr. A. G. De Sanctis, Dr. W. W. Lasher and Dr. M. C. Pease.



## ARCHIVES OF SURGERY

When growth in the blood culture had been recognized on May 3, a transfusion of 80 cc. was given, and 10,000 units of the concentrated serum of the New York State Department of Health was injected intramuscularly. The dose of serum was repeated on May 4 at 10 a. m. At this time the neck was stiff and the eyes glazed. An erysipelatous rash extended downward from the nose, and there were separate areas of it on the scalp and leg. Respiration became labored and the pulse irregular. Death occurred at 7:10 p. m. Necropsy revealed organizing subdural hemorrhage, probably from injury at birth, acute purulent meningitis, serous otitis media and mastoiditis. The heart valves were normal. The site of the original invasion was not recognized.

CASE 2 (chart 2).—J. D. B., a boy, aged 27 months, became ill with fever on Feb. 25, 1933, and on March 1 there were vomiting and diarrhea. On March 2 a

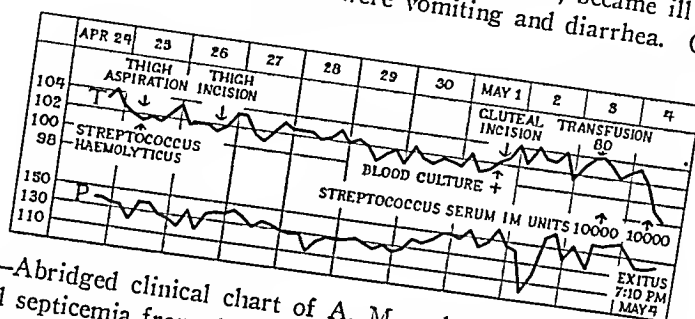


Chart 1.—Abridged clinical chart of A. M., a boy, aged 19 days. Apparently this baby had septicemia from the start. A positive blood culture was obtained on May 1, and the serum was administered on May 3 and 4. The child died on May 4.

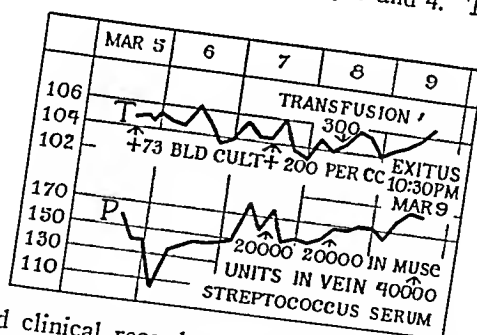


Chart 2.—Abridged clinical record of J. D. B., a boy, aged 27 months. This baby had a positive infection of the blood stream on admission. The serum was administered on March 7 and 8 intravenously and on March 9 by intramuscular injection. The child died on March 9.

maculopapular rash appeared, and this remained when the patient came to the hospital. On March 4 the temperature reached 106 F., and the child was admitted to the hospital on the following day. The urine showed protein (3+), and a systolic heart murmur was recognized. The eruption was in part purpuric. Blood culture taken at once on March 5 yielded 73 colonies of hemolytic streptococci per cubic centimeter of blood. When this result was recognized, on March 7, another blood culture was taken and one ampule (20,000 units) of concentrated streptococcus serum was injected intramuscularly. This dose was repeated the next day immediately after a transfusion of 300 cc. On March 9 an intravenous injection of two ampules (40,000 units) was given at 4 p. m. Signs of bronchopneumonia and of meningitis appeared, and the child died at 10:30 p. m.

Necropsy disclosed septic petechiae of the serous membranes, mucous membranes and skin, active vegetative mitral endocarditis, septic emboli in the myocardium and purulent infarcts of the spleen and kidneys. Examination of the head was not permitted.

CASE 3 (chart 3).—N. L., a boy, aged 31 months, has a longer record. He became ill on March 19, 1933, awakening during the night with severe pain in the right leg. Four days later the mother recognized swelling of the right foot and leg and a reddened area on the ankle. The temperature had ranged between 102 and 104 F. On March 24 the child was admitted to the hospital. At this time the swelling and inflammation of the right leg were more pronounced. The right forearm and wrist were also swollen and painful. The pharynx was bright red, and

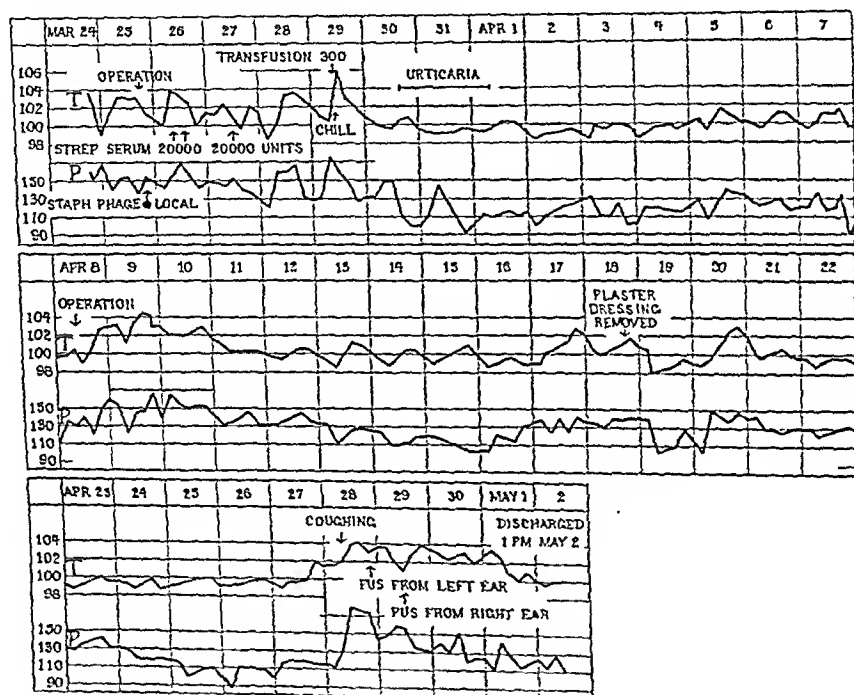


Chart 3.—Abridged clinical record of M. L., a boy, aged 31 months. This child was operated on for osteomyelitis of the right arm and right leg on March 25. On the assumption that the infection was due to the staphylococcus, bacteriophage was applied immediately after the operation. The streptococcus serum was given on March 26 and March 27, the first dose subcutaneously and the second into the muscle. The patient did very well until April 27, when bilateral otitis media developed. The nature of the infecting microbe was not ascertained, but it is probable that the immunity to the streptococcus had disappeared during the period of one month.

the cervical lymph nodes were enlarged. Both ear drums were injected and slightly bulging.

The abridged clinical record is shown in chart 3. On March 25, at 6:30 p. m., pus was aspirated from the right ankle, and following this the right forearm and right leg were incised. In the forearm there was a deep abscess extending to the anterior surface of the pronator quadratus muscle but not involving the bones or

the wrist joint. In the leg there was erosion of periosteum at the lower end of the fibula, and the tibial periosteum was elevated with pus and small hemorrhages beneath it. An abscess containing about 120 cc. of pus extended about the right ankle, involving the tendon of the pronator longus muscle but not the joint cavity. Multiple openings were drilled in the lower end of the tibia, the periosteum was incised, and drainage of the soft tissues was established. Staphylococcus bacteriophage was at once applied as a wet dressing on the assumed diagnosis of staphylococcic osteomyelitis.

On the following day the microscopic and cultural examination of the specimens of exudate revealed the certain presence of hemolytic streptococci; staphylococci could not be recognized then or later. The child was therefore given 0.2 cc. of the concentrated streptococcus serum subcutaneously, and five hours later the remainder of the ampule intramuscularly, making a total of 20,000 units on March 26. On March 27 another intramuscular dose of 20,000 units was given. Transfusion on March 29 was followed by a chill and a rise in temperature to 106 F. There was a moderately severe serum rash on March 30, which faded by April 1. The clinical course was highly satisfactory until April 8, when, under ether anesthesia, the wounds were revised and Orr dressing with plaster bandages were applied. Another disturbance on April 27 was evidently due to an infection of the upper respiratory tract complicated by bilateral purulent otitis media, with streptococci present. When this subsided the patient was allowed to go home.

The serum administered on March 26 and 27 seemed to have exercised a beneficial influence on the infectious lesions in the forearm and leg. However, it was obviously inadequate to prevent the development of the respiratory infection a month later. Whether the serum contributed something of value in control of the original streptococcic infection may be debated. At any rate, one could not expect a more favorable course of the disease than that shown by this patient after March 30. Those of us who had opportunity to observe the patient were willing to credit the serum with a favorable influence.

CASE 4 (chart 4).—D. S., a boy, aged 3 years and 7 months, had been ill with a cold at home since Jan. 4, 1932. On January 14 enlarged bilateral cervical nodes were observed, and the temperature reached 106 F. After this the child was kept in bed. On January 24 he had a chill, his temperature rose to 105.6 F., and he complained of pain in the right knee. He was admitted to the hospital at 4:30 p. m. on this day. At this time both ear drums were congested, the pharynx was red, and the cervical lymph nodes were firm and moderately enlarged. The child favored the right knee, but on physical examination it was found to be normal.

A blood culture taken at 8 p. m., January 24, revealed hemolytic streptococci after thirty-six hours. On January 25, because of some rigidity of the neck, limitation of movement of the right leg and the recognition of some problematic red spots on the skin, a spinal tap was done. This yielded a normal spinal fluid. Roentgenologic study disclosed capsular distention of the right hip joint on January 25 and of the right knee joint on January 27. Blood culture taken on January 26 was again positive. Transfusions were given on January 28 and 30. The spinal fluid was found to be infected with streptococci on January 28 and again on February 1. On this day the condition appeared desperate. The patient was unconscious, and there was slight general cyanosis. The concentrated anti-streptococcus serum was administered, one ampule of 20,000 units into the spinal canal and a similar dose intravenously. Larger doses were administered on February 2 and 3. There was no evident response. The patient died early in the morning of February 4. Necropsy disclosed bilateral otitis media and mastoiditis,

bilateral purulent thrombosis of the lateral sinuses, diffuse purulent meningitis, bilateral cervical adenitis, bronchopneumonia and general sepsis.

CASE 5 (chart 5).—C. M., a girl, aged 5 years, had an infection of the upper respiratory tract with cough and a rise in temperature to 102 F. in May 1933. At about this time she complained of pain in the left arm. Roentgenologic study at that time gave negative results. About a week later an abscess on the outer aspect of the left arm was incised, and a second roentgenologic examination in the following week disclosed changes in the upper portion of the humerus. On June 22 an operation was performed for osteomyelitis with pathologic fracture of the neck of the left humerus. On August 8 a roentgenogram revealed osteomyelitis of the entire shaft of the humerus, with apparent sequestration of the upper half. At this time the child was brought to New York.

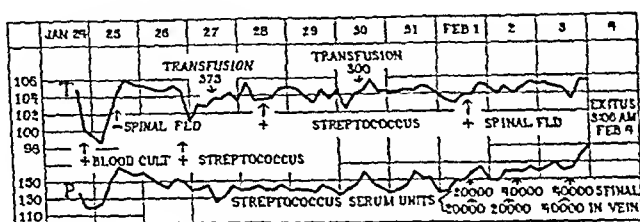


Chart 4.—Abridged clinical record of D. S., a boy, aged 3 years and 7 months. This child had an infection of the blood stream on admission to the hospital on January 24, and on January 28 the spinal fluid was found infected. Serum was given on February 1 and the following days. The child died early in the morning of February 4.

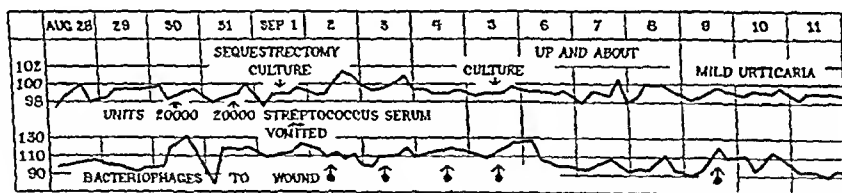


Chart 5.—Abridged clinical record of C. M., a girl, aged 5. This girl had osteomyelitis of the left humerus with sequestration. Serum was given intravenously for two days preceding the removal of the necrotic bone. The post-operative course was highly satisfactory, and the wound has gone on to complete healing without further incision. There was a moderate serum reaction in this case evident on September 9.

She was admitted to the Post-Graduate Hospital on August 17, at which time the upper half of the left arm was swollen, red and painful, with marked limitation of motion. There was a granulating incision on the outer aspect of the upper part of the left arm and also a draining left axillary sinus. Roentgenologic study at this time showed extensive old osteomyelitis involving almost the entire shaft of the humerus. The upper end of the old shaft was already separated as a sequestrum, with debris surrounding it. The middle and lower thirds of the old shaft appeared in the process of sequestration but not yet separated. A culture taken on August 18 from the draining sinus yielded pure growth of hemolytic streptococci. On August 21, a transfusion of 315 cc. was given, and the arm was immobilized

by a plaster dressing. It was deemed unwise to attempt sequestrectomy at this time because of the streptococcic infection, although the general condition of the patient was good.

A brief portion of the abridged clinical record is shown in chart 5. At the request of the surgical consultant, a preliminary treatment with streptococcus serum was undertaken in preparation for the operation. On August 30, a minute intracutaneous injection of the serum gave no evidence of hypersensitiveness. This was followed by a subcutaneous injection of 0.5 cc. of the serum and then after an hour by the intravenous injection of the remainder of the ampule making a total of 20,000 units for this day. On August 31 another ampule of 20,000 units was given intravenously. The sequestrectomy was performed on the following day with only slight disturbance to the patient. Her appetite was good on September 2, and on September 6, five days after the operation, she was up and about the ward. An itching erythema appeared on September 7 or 8 on the right arm and neck, and by September 9 this had extended to the face and to the abdominal skin, apparently a mild serum eruption.

Cultures from the exudate about the sequestrum, taken on September 1, yielded *Staphylococcus aureus* as well as streptococci. Subsequently other bacteria appeared in the drainage from the wound and sinus. On this account bacteriophages were applied as a wet dressing. The patient still remains under observation in good general condition with sinuses entirely healed. The point of chief interest for the present report has to do with the prophylactic use of the serum in preparation for surgical operation on a field infected with hemolytic streptococci.

#### COMMENT

Physicians who do not employ antistreptococcus serum will see in the record of these five patients little to encourage them in its use. On the other hand, it appears that a fair test of the value of the serum has not been afforded here.

In the first patient, A. M., the fever appeared on April 19, when the baby was 2 weeks old, and the first dose of serum was administered on May 3 after a blood culture taken on May 1 was recognized as positive. This was on the day before death, at a time when meningitis must have already been present, according to necropsy.

The second patient, J. D. B., became ill with fever on February 25, and the first administration of the serum occurred on March 7, when the blood culture taken two days before had shown positive growth. Necropsy on March 9 revealed an acute vegetative mitral endocarditis with associated septic complications.

The fourth patient, D. S., was ill from January 4, with a temperature of 106 F. on January 14. The serum treatment was initiated on February 1, eight days after the positive blood culture was taken on January 24 and four days after the recognition of meningitis on January 28.

The third patient, N. L., had been ill only since March 19. After the operation for osteomyelitis on March 25 the surgeon asked for the assistance of bacteriotherapy because of the impression that the disease was due to the staphylococcus. When the bacteriologic studies disclosed

the true etiology, the streptococcus serum was administered on March 26 and 27. There was a moderately severe serum rash four days later, but in other respects the behavior of the patient left little to be desired for nearly a month. One cannot be sure of the part played by the serum, but the record is at least suggestive. Apparently the protective effect of the serum had disappeared by April 27, or else the extension of infection into the ears was due to some unrelated organism. We are inclined, however, to believe that the continued frequent administration of small doses of the serum would have been a good thing in this case.

The fifth patient had already suppressed the original invasion of the blood stream. In her case the serum was employed as a safeguard against lighting up a streptococcic infection still persisting in the arm. The actual result was all that had been desired. Whether the patient would have done as well without the serum remains undetermined.

In our experience specific bacteriotherapeutic measures are most often instituted after too much delay. The first, second and fourth of these four patients represent examples. In the case of the third patient the earlier administration of the serum came about through a misapprehension. The bacteriologists were called in consultation in the hope of treating a staphylococcic infection with bacteriophage and once this contact with the patient had been made, the early administration of streptococcus serum became possible.

#### CONCLUSIONS

1. In vegetative endocarditis due to the hemolytic streptococcus and in meningitis coupled with bacteremia due to the same organism, the therapeutic use of antistreptococcus serum, in our hands, has not been successful.
2. The administration of the concentrated antistreptococcus serum of the New York State Department of Health in one case of streptococcic osteomyelitis was followed by a favorable course of the disease.
3. In a second patient with osteomyelitis the injection of the serum for two days preceding a sequestrectomy was followed by an unusually fortunate surgical result.

# FIFTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL DEFORMITIES AND DISTURBANCES OF GROWTH

*Comparative Study of Congenital Coxa Vara and Coxa Plana.*—Carnitz<sup>1</sup> made histologic examinations of three specimens from the femoral head in congenital coxa vara and compared these with the pathologic changes recorded in coxa plana. He concluded that, histologically, infantile coxa vara and coxa plana cannot be differentiated. They appear to be variations of the same developmental disturbance during growth.

*Anatomic Basis and Origin of the Cross-Striations in the Metaphyses of Growing Bones.*—Hamperl<sup>2</sup> studied the broad bands of cross-striation in growing bones resulting after intoxication from phosphorus, arsenic or lead and from syphilis and deficiency of vitamin D. He excluded from study the thin transverse lines which he observed in roentgenograms with each year of growth. A histologic examination of these broad metaphyseal bands was made in two cases. The bands consisted of a thick network of bony lamellae enclosing the remains of calcified cartilage. These bands apparently had formed at the epiphyseal line and on growth had moved out into the metaphysis. They resulted from a disturbance in enchondral ossification. No osteoclasts were seen in these areas. In mild cases the bands represented delayed absorp-

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This report of progress is based on a review of 213 articles selected from 467 titles appearing in medical publications approximately between April 1 and July 30, 1934. Only those which seemed to represent progress were chosen for review.

1. Carnitz, H.: Acta chir. Scandinav. 73:521, 1934.

2. Hamperl, H.: Ztschr. f. Kinderh. 56:324, 1934.

tion of the calcified cartilage ground substance. The approximate duration of the disturbance could be calculated by the distance of the band from the epiphysis, since in early life long bones such as the tibia grow about 3 mm. a month in summer and 2 mm. a month in winter.

[ED. NOTE.—These observations are interesting. In the experience of the editors, growth at the epiphyseal line is not as constant as this article suggests.]

#### DISTURBANCES IN OSSEOUS METABOLISM

*Vitamin D Milk.*—Wyman<sup>3</sup> stated that milk containing 432 U. S. P. revised units of vitamin D per quart (946 cc.) automatically prevents the occurrence of rickets. The milk should be given in the summer as well as in the winter in climates similar to that of New England. While 382 units amply supply the need for vitamins, milk of lesser potency may be adequate.

Kramer and Gittleman<sup>4</sup> reported that as little as 108 U. S. P. revised units of vitamin D per day produced a definite curative action in patients with rickets. With the amounts fed there was no difference in effectiveness between vitamin D milk prepared by direct irradiation and similar milk produced by feeding cows irradiated yeast.

Wilson<sup>5</sup> made a clinical study of the efficacy of milk fortified with 405 U. S. P. revised units of vitamin D per quart in the form of cod liver oil concentrate in preventing rickets. Thirty-three artificially fed infants (two thirds of them were Negro or Italian) were selected for study. Most of these were under 8 weeks of age in this period. Of the thirty-three, fourteen remained normal, slight rickets developed in seventeen and a moderate degree of rickets appeared in two. The conclusions were that since the amount of vitamin D necessary to prevent rickets is dependent on the rate of growth and since the rate of growth does not conform to the daily consumption of milk, fortified milk should contain enough vitamin D to afford protection when considerably less than a quart is consumed per day. Four hundred and five units per quart did not prove sufficient. How many units are necessary must be shown by future studies.

[ED. NOTE.—In the past few years many different ways of supplying vitamin D to infants have been proposed. Since they are all simpler than the administration of cod liver oil, there has been a tendency to adopt them too quickly. As the preceding articles show, the status of milk as a substitute for cod liver oil is not yet definitely known.]

3. Wyman, E. T.: *New England J. Med.* 209:889, 1933.

4. Kramer, B., and Gittleman, I. F.: *New England J. Med.* 209:906, 1933.

5. Wilson, W. R.: *Prevention of Rickets by Milk Fortified with Vitamin D (150 Steenbock Units of Vitamin D per Quart)*, *J. A. M. A.* 102:1824 (June 2) 1934.



*Hunger Osteopathy; Juvenile and Late Rickets.*—From a clinical investigation, Crawford and Cuthbertson<sup>6</sup> concluded that the essential difference between the metabolism in a case of hunger osteopathy and one of rachitic condition was that the mineral salts were stored rapidly without the administration of irradiated ergosterol in the first case, whereas in the second irradiated ergosterol had to be added before an appreciable retention was secured. They considered that although hunger osteopathy and late rickets (osteomalacia) are not necessarily identical in their nutritional origin, both occur with a deficiency of vitamin D.

*Calcium and Phosphorus Metabolism in Diseases of the Thyroparathyroid Apparatus.*—From a careful investigation of cases of hyperthyroidism, Hansman and Wilson<sup>7</sup> concluded that a direct catabolic effect of thyroxine on the calcium deposits in bone, such as has been claimed to exist, cannot be the cause of the excessive mobilization and excretion of calcium and phosphorus. In a second paper, Hansman<sup>8</sup> concluded that the beneficial effect of the administration of vitamin D in cases of hypoparathyroidism is not due to better absorption of calcium or of organic phosphorus or of the product of calcium times phosphorus. He suggested that vitamin D acts by making the calcium available for tissue metabolism.

*Relation of Thyroid, Suprarenal Glands and Islands of Langerhans to Malacic Diseases of Bone.*—Golden and Abbott<sup>9</sup> stated that the evidence at hand indicated that skeletal decalcification of a degree sufficient to be of differential diagnostic importance on the roentgenogram and attributable to endocrine disturbances may be encountered in hyperthyroidism, but not in hypothyroidism, disease of the suprarenal glands or diabetes in adults. In diabetes in children decalcification of the bone was occasionally found, for which acidosis or malnutrition or both were probably responsible.

#### TUBERCULOSIS

*Treatment of Surgical Tuberculosis with Splenic Extract.*—After following under carefully controlled conditions twenty patients with surgical tuberculosis, ten of whom received splenic extract, Barr<sup>10</sup> concluded that there was insufficient evidence of a therapeutic effect of splenic extract on the course of surgical tuberculosis.

*Tuberculosis of Shafts of Long Bones.*—Van Gorder<sup>11</sup> reported six cases of tuberculosis of shafts of long bones in Chinese. The age ranged from 9 to 21 years. The clinical, pathologic and roentgenologic features

6. Crawford, A. M., and Cuthbertson, D. P.: *Quart. J. Med.* **3**:87, 1934.

7. Hansman, F. S., and Wilson, F. H.: *M. J. Australia* **1**:37, 1934.

8. Hansman, F. S.: *M. J. Australia* **1**:81, 1934.

9. Golden, R., and Abbott, H.: *Am. J. Roentgenol.* **30**:641, 1933.

10. Barr, J. S.: *J. Bone & Joint Surg.* **16**:173, 1934.

11. Van Gorder, G. W.: *J. Bone & Joint Surg.* **16**:269, 1934.

of the disease were discussed. The bones involved were: ulna (four cases); tibia (one case), and radius (one case). Five patients were cured by subperiosteal resection of the diseased bone. The sixth patient did not report for the study of the end-results but was presumably well.

#### POLIOMYELITIS

*Poliovmyelitis in California.*—Apropos of the epidemic of anterior poliomyelitis in Los Angeles in June 1934, an editorial<sup>12</sup> in *The Journal of the American Medical Association* answered two questions, universally asked when the incidence of infantile paralysis is higher than normal: 1. Is it dangerous to travel through a district having a high incidence? There is a definite danger, particularly for children under 6 years of age. It is impossible to protect a child against contact, since the disease can presumably be distributed through carriers. This danger holds until the advent of really cool weather. 2. Should mass immunization of apparently well children be carried out? Neither whole blood nor convalescent serum has been used sufficiently in controlled experiments to provide data on this subject. If such experiments are made, accurate records should be kept so as to determine future practice.

*Creatine-Creatinine Exchange in Poliomyelitis and Its Influence by Glycine.*—Gross<sup>13</sup> determined the creatine-creatinine excretion in seven cases of poliomyelitis during the period of regeneration before and after the administration of glycine. The spontaneous high excretion of creatine bore a certain relationship to the severity of the disease. After the administration of from 15 to 20 Gm. of glycine a day, a definite increase in the excretion of creatinine in the urine was observed, while the amount of preformed creatine did not measurably change. The increase varied with the patient and with the amount of glycine administered. The appearance of extra creatininuria after the administration of glycine was not specific for muscular dystrophy. Gross suggested that daily doses might favorably influence the period of regeneration in poliomyelitis.

[ED. NOTE.—Various reports on the use of glycine to improve the muscular metabolism have appeared in the literature, a few of which have been reviewed in earlier reports of progress. The question of its therapeutic value in such conditions is still sub judice.]

#### CHRONIC ARTHRITIS

*Autogenous Vaccines in Rheumatoid Arthritis.*—Short and his co-workers<sup>14</sup> studied the action of autogenous vaccines in patients with chronic arthritis and in normal controls. They concluded that in arthritis

12. Poliomyelitis in California, editorial, J. A. M. A. **102**:2106 (June 23) 1934.

13. Gross, W.: Ztschr. f. klin. Med. **126**:152, 1934.

14. Short, C. I.; Dienes, L., and Bower, W.: Am. J. M. Sc. **187**:615, 1934.

there is no allergy to streptococci, as shown by skin reactions, comparable to that in certain other chronic infectious diseases. Skin tests did not permit a satisfactory selection of specific bacteria for vaccine therapy. Variations in the skin reactions were thought to be due to a difference in dermal irritability, to natural toxicity of certain bacterial species or to sensitization to certain bacterial groups. The authors expressed the belief that the therapeutic effect of autogenous vaccines was nonspecific.

*Histologic Changes in the Knee Joint with Advancing Age; Relation to Degenerative Arthritis.*—Parker and his colleagues<sup>15</sup> studied one hundred knee joints of elderly persons and found that the synovial membrane, the articular cartilage and the subchondral bone undergo certain changes with age comparable to degenerative or hypertrophic arthritis. In some cases hyaline cartilage showed the power to regenerate. The synovial membrane was normal except in those cases in which there was damage to the articular cartilage. Other changes in the cartilage and bone were described. The bony exostoses in traumatic joints were found to be due either to a projection of bone and cartilage over the surface of the joints or to a depression in the cartilage, thus giving the appearance of a bony outgrowth.

#### THE SPINE

*Sciatica and the Sacro-Iliac Joint.*—After performing anatomic studies on the relationship of the piriformis muscle, the sacro-iliac joint and the sciatic nerve, Freiberg and Vinke<sup>16</sup> found that prolonged spasm of the piriformis muscle may produce circulatory disturbances in the sciatic nerve. These disturbances in time produce adhesions between the sciatic nerve and the piriformis muscle, especially as in many instances the sciatic nerve passes through the belly of the piriformis muscle. On this basis, the relief from sciatic pain following manipulative measures may be explained on the basis of the release of adhesion between the piriformis muscle and the sciatic nerve and the stretching of a contracted piriformis muscle. The authors did not attempt to explain all sciatic pain on this basis.

*Relaxation of the Pelvic Joints in Pregnancy.*—According to Abramson and his co-workers,<sup>17</sup> relaxation of the pelvic joints is a normal physiologic process beginning in the first half of pregnancy and affected little by parturition. In their patients the return to normal was

15. Parker, F., Jr.; Keefer, C. S.; Myers, W. K., and Irwin, R. L.: *Histologic Changes in Knee Joint with Advancing Age: Relation to Degenerative Arthritis*, Arch. Path. **17**:516 (April) 1934.

16. Freiberg, A. H., and Vinke, T. H.: *J. Bone & Joint Surg.* **16**:126, 1934.

17. Abramson, D.; Roberts, S. M., and Wilson, P. D.: *Surg., Gynec. & Obst.* **58**:595, 1934.

usually complete in from three to five months post partum. An abnormal relaxation was found in 25 per cent of the patients examined. The authors advised treatment with a pelvic sling during recumbency and with a sacro-iliac belt during the ambulatory stage. They stressed the importance of treatment to prevent late symptoms of strain of the pelvic joints.

*Oblique View for the Demonstration of the Articular Facets in Cases of Lumbosacral Backache and Sciatic Pain.*—Ghormley and Kirklin<sup>18</sup> described in detail their technic for taking oblique views of the lumbosacral region. They stated that these views gave them an opportunity to study in detail the articular facets of the weak back in the lower part of the lumbar region. They emphasized the importance of the facets in the production of pain in the lower part of the back and sciatic pain. The transverse axis of the pelvis is tilted at an angle of 32 degrees to the film, and an anteroposterior roentgenogram is taken. The tube is centered perpendicularly to the film, directly above the mid-point of Poupart's ligament on the elevated side.

*The Lumbosacral Junction.*—Mitchell<sup>19</sup> discussed the lumbosacral junction, its anatomy and physiology and certain defects in this region accounting for disability of the lower part of the back. He described a method of accurately measuring the lumbosacral angle. The article furnishes an excellent review of the subject and is well worth preservation as a reference to the anatomy and function of the lumbosacral junction.

*Lateral Tilt of the Pelvis in Children.*—That lateral tilt of the pelvis is sometimes due to a primary malrotation of the fifth lumbar vertebra on the sacrum was stated by Cyriax.<sup>20</sup> The condition is more common in females and is caused by a sudden twist of the trunk, as while playing games, or by actual trauma. The rotary movement of the spine is checked by the inertia of the pelvis at the lumbosacral joint. If the joint is not strong enough or is caught unawares, a rotary displacement of the fifth lumbar vertebra on the sacrum ensues. Immediate replacement may occur or the displacement may persist. In the latter case one side of the pelvis is tilted downward and forward and can be straightened only by the development of lumbar scoliosis. Treatment is by derotation without anesthesia. After-treatment consists of exercises if a weakness of the muscles or an actual scoliosis exists.

#### CIRCULATORY DISTURBANCES OF THE EXTREMITIES

*Effect of Alternate Suction and Pressure on Blood Flow to the Lower Extremities.*—In carefully carried out experiments Landis and

18. Ghormley, R. K., and Kirklin, B. R.: *Am. J. Roentgenol.* **31**:173, 1934.

19. Mitchell, G. A. G.: *J. Bone & Joint Surg.* **16**:235, 1934.

20. Cyriax, E.: *Brit. J. Child. Dis.* **30**:274, 1933.

Gibbon<sup>21</sup> found that alternating pressure and suction applied to an extremity definitely increase the peripheral blood flow to the extremity in spite of advanced organic disturbance.

*Vasodilatation of the Extremities.*—In considering peripheral vascular disease it is becoming increasingly important to differentiate clearly between organic occlusion of the vessels and vascular spasm, according to an editorial in *The Journal of the American Medical Association*.<sup>22</sup> The several tests used to determine peripheral vasodilatation are similar in principle, all employing thermo-electric measurements of the surface temperature. The procedures used have not been simple and all have had their contraindications. In 1933, however, an exceedingly simple method of producing vasodilatation was investigated by Gibbon and Landis.<sup>23</sup> They observed that immersing the forearms and hands in warm water produces vasodilatation in the lower extremities. Immersion for a half-hour is sometimes necessary, but even so the method is much simpler than the injection of foreign protein or the induction of spinal or general anesthesia. In every instance in which it was applied to a normal subject the surface temperature exceeded 88.7 F., which is the minimum response to anesthesia. This method was checked with the older, more complicated procedures, and similar results were obtained in normal persons and persons with a pathologic condition. Another promising procedure is the study of the peripheral pulse volume. Such a study can be made with the plethysmometer described by Scupham and Johnson.<sup>24</sup> The movement records the pulse volume wave graphically, so that it can be kept as a permanent record.

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21. Landis, E. M., and Gibbon, J. H., Jr.: *J. Clin. Investigation* **12**:925, 1933.

22. Vasodilatation of the Extremities, editorial, *J. A. M. A.* **102**:932 (March 24) 1934.

23. Gibbon, J. H., Jr., and Landis, E. M.: *J. Clin. Investigation* **11**:1019, 1932.

24. Scupham, G. W., and Johnson, C. A.: *Peripheral Vascular Phenomena: Peripheral Pulse Volume in Occlusive Arterial Diseases*, *Arch. Int. Med.* **52**:877 (Dec.) 1933.

(To be concluded)

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